Physical Activity

and

Musculoskeletal Health

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

University of Tasmania (February, 2009)

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ABSTRACT

Population ageing is unprecedented and enduring. By 2050, the proportion of those aged over 65 would have increased from 13% to 26%. As the population ages, the prevalence of chronic diseases that disproportionately affect the elderly will markedly increase. Osteoarthritis and osteoporosis, including resulting fractures are two such diseases. Physical activity (PA) is an important risk factor for both of these diseases but many questions remain unanswered. This thesis examines how PA and exercise interacts with features of falls, osteoarthritis and osteoporosis.

In a population based sample of 50-80 year olds (n=850) followed over 2.6 years, self reported functional ability and pain, and to a lesser extent stiffness (but not radiographic osteoarthritis) have modest but independent associations with physiological predictors of falls risk suggesting it is symptoms not radiographic changes that increase falls risk. In addition, ambulatory activity is positively associated with hip bone density in both sexes which appears most important in those aged over 65 years. However, the associations for spine bone density are both weaker and inconsistent.

In a convenience sample of 26-61 year olds (n=325) followed over two years, we found knee cartilage volume and tibial plateau area are dynamic structures that can respond to physical stimuli. Greater muscle strength and endurance fitness, especially in women, protects against cartilage loss, but also results in a maladaptive enlargement of subchondral bone in both sexes, suggesting PA may have both good and bad effects on the knee.

1,434 children, aged 7-15 years, were measured in 1985 and approximately 20 years later. We found childhood fitness levels, particularly in females and in the early pubertal years, predicts adult bone mass, while BMI predicts bone mass in males only. These results suggest that increased skeletal loading in childhood leads to an increase in peak bone mass independent of current loading.

In 183 children examined at age 8 and 16, bone mass measured by dual x-ray absorptiometry (DXA) is a good predictor of upper limb fracture risk during puberty. DXA measures track moderately to strongly from childhood to adolescence. Tracking is independent of linear growth and sex indicating bone mineralisation and growth are under largely separate mechanistic control. Body composition is the main predictor of altered tracking but environmental factors, such as having been breastfed, sports participation, fitness and inhaled corticosteroid use also appear important.

In conclusion, this series of related studies shed considerable insight onto the role that PA and exercise play in preventing osteoarthritis and osteoporosis. In particular, childhood appears the most opportune time to prevent osteoporosis but later life is also important while for osteoarthritis, results remain less certain for structural change.

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LIST OF PUBLICATIONS

PUBLICATIONS ARISING FROM THE THESIS

Chapter 4:

Foley S, Lord SR, Srikanth V, Cooley H, Jones G 2006 Falls risk is associated with pain and dysfunction but not radiographic osteoarthritis in older adults: Tasmanian Older Adult Cohort study. Osteoarthritis Cartilage **14**(6):533-9.

Chapter 5:

Foley S, Ding C, Cicuttini F, Jones G 2007 Physical activity and knee structural change: a longitudinal study using MRI. Med Sci Sports Exerc **39**(3):426-34.

Chapter 6:

Foley S, Quinn S, Dwyer T, Venn A, Jones G 2008 Measures of childhood fitness and body mass index are associated with bone mass in adulthood: a 20-year prospective study. J Bone Miner Res **23**(7):994-1001.

Chapter 7:

Flynn J*, Foley S*, Jones G 2007 Can BMD assessed by DXA at age 8 predict fracture risk in boys and girls during puberty?: an eight-year prospective study. J Bone Miner Res **22**(9):1463-7. *Equal first author.

Chapter 7:

Jones G, Flynn J, Foley S 2008 Site Specificity of Fracture Prediction in Children. J Bone Miner Res **23**(5):771.

Submitted manuscripts

Chapter 8:

Foley S, Quinn S, Jones G. Tracking of bone mass from childhood to adolescence and factors that predict deviation from tracking. *Bone*. In press.

Chapter 9:

Foley S, Quinn S, Jones G. Pedometer measured ambulatory activity and bone mass: A population based longitudinal study in older adults. *Journal of the American Medical Association.*

SCIENTIFIC PRESENTATIONS ARISING FROM THE THESIS

ORAL PRESENTATIONS

2006 Australian Rheumatology Association, Perth, Western Australia

Physical Activity and Knee Structural Change: A Longitudinal Study using MRI

2006 Australian and New Zealand Bone and Mineral Society/ International Osteoporosis Federation, Port Douglas, Queensland

Measures of Childhood Fitness and BMI are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study

2007 Australian Epidemiology Association, Hobart, Tasmania

Measures of Childhood Fitness and BMI are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study

2007 Australian and New Zealand Bone and Mineral Society, Queenstown, New Zealand

Tracking of Bone Mass: Childhood to Adolescence

POSTER PRESENTATIONS

2007 Australian and New Zealand Bone and Mineral Society, Queenstown, New Zealand

Body Composition and Bone Mass: Childhood to Adolescence

2007 American Society of Bone and Mineral Research, Honolulu, Hawaii

Measures of Childhood Fitness and BMI are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study

2008 Australian and New Zealand Bone and Mineral Society, Melbourne, Victoria

Pedometer measured steps per day and bone mass: A population based study in older adults

AWARDS RESULTING FROM THESIS MATERIAL

2006	Awarded travel grant by Australian Rheumatology Association (ARA) to attend ARA meeting in Perth for presentation entitled "Physical Activity and Knee Structural Change: A Longitudinal Study using MRI"
2006	Awarded travel grant by Australian and New Zealand Bone and Mineral Society (ANZBMS) to attend ANZBMS meeting in Port Douglas for presentation entitled "Measures of Childhood Fitness are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study"
2006	Awarded ANZBMS/IOF Amgen outstanding abstract award for abstract entitled "Measures of Childhood Fitness are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study"
2007	Awarded Australian Epidemiology Association outstanding abstract award for abstract entitled "Measures of Childhood Fitness are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study"
2007	Awarded travel grant by ANZBMS to attend ANZBMS meeting in Queenstown for presentation entitled "Tracking of Bone Mass: Childhood to Adolescence"
2007	Awarded Rodger Mellick Young Investigator award (clinical) for presentation entitled "Tracking of Bone Mass: Childhood to

Adolescence". Australian and New Zealand Bone and Mineral Society. Queenstown.

2007 Awarded travel grant by American Bone and Mineral Society (ASBMR) to attend ASBMR meeting in Honolulu for presentation entitled "Measures of Childhood Fitness are associated with Calcaneal Quantitative Ultrasound in adulthood: A 20 year Prospective Study"

2008 Awarded Menzies Research Institute 2007 Postgraduate Student Prize

2008 Awarded travel grant by ANZBMS to attend ANZBMS meeting in Melbourne for presentation entitled "Pedometer measured steps per day and bone mass: A population based study in older adults"

LIST OF ABBREVIATIONS

aBMD	areal bone mineral density
ASHFS	Australian Schools Health and Fitness Survey
BA	bone area
BMAD	bone mineral apparent density
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BUA	broadband ultrasound attenuation
CIs	confidence intervals
CV	cartilage volume or coefficient of variation
DXA	dual x-ray absorptiometry
FM	fat mass
HR	hazards ratio
HRT	hormone replacement therapy
ICC	intraclass correlation coefficient
ICS	inhaled corticosteroids
JSN	joint space narrowing
LM	lean mass
MRI	magnetic resonance imaging
OA	osteoarthritis
OR	odds ratio
PAA	pedometer determined ambulatory activity
PPA	Physiological Profile Assessment

PWC_{170}	physical work capacity at 170 beats/min
QUI	quantitative ultrasound index
QUS	quantitative ultrasound
RA	rheumatoid arthritis
RCT	randomised controlled trial
ROA	radiographic osteoarthritis
SD	standard deviation
SMD	standard mean difference
SOS	speed of sound
TASOAC	Tasmanian Older Adult Cohort Study
VO_{2max}	maximal volumetry oxygen uptake
WOMAC	Western Ontario and McMaster Universities Index of Osteoarthritis

TABLE OF CONTENTS

SYNOPSIS

By 2050, the proportion of the population aged over 65 will have increased from 13% to 26%. As the population ages, the prevalence of falls, osteoarthritis and osteoporosis, including resulting fractures will increase markedly. These conditions constitute a major health problem due to their large contribution to illness, pain and disability, high frequency and resulting economic burden. Physical inactivity is an important risk factor risk for falls, osteoarthritis (OA) and osteoporosis but many questions remain unanswered.

Chapter 1 explores the epidemiology of falls, OA and osteoporosis, including resulting fractures.

Chapter 2 lists the research questions to be addressed.

Chapter 3 briefly describes the four studies that were utilised in this thesis and the study factors pertinent to each research question.

Chapter 4 reports the cross-sectional association between knee and hip radiographic osteoarthritis (ROA), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measured knee pain, stiffness and functional ability and objectively measured physiological falls risk predictors. Overall, the study population, 850 randomly selected men and women aged 50-80 years were at a mild risk of falling. In multivariable analysis, the WOMAC function and pain score was significantly associated with reaction time, balance, proprioception, knee extension strength, and edge contrast sensitivity. Stiffness was associated with knee extension strength and edge contrast sensitivity. Males had a dose response association between the global

WOMAC score and falls risk ($r = 0.17$, $p<0.001$). Those who reported a global WOMAC score of 50 and above had a higher risk of falling compared to those with a score below 50 (z score: 0.53 v 0.14, $p<0.001$). Hip joint space narrowing (JSN) was significantly associated with knee extension strength ($r = -0.10$, $p = 0.003$), however no other significant associations were observed between ROA and falls risk predictors. In conclusion, self reported functional ability and pain, and to a lesser extent, stiffness (but not knee and hip ROA), had a modest but independent association with physiological predictors of falls risk.

Chapter 5 described the associations between physical activity (PA) and structural changes of the knee joint as assessed by magnetic resonance imaging (MRI) in adult male and female subjects. The results showed lower limb muscle strength at baseline was positively associated with both %/year changes in total cartilage volume ($r=0.13$) and lateral and total-tibial plateau area ($r=0.15$ and $r=0.17$) but not other sites, while change in muscle strength was negatively associated with annual changes in lateral and total-tibial plateau area ($r=-0.13$ and $r=-0.17$). In females only, physical work capacity at 170 beats/min (PWC_{170}) at baseline was negatively associated with %/year changes in lateral and total cartilage volume ($r=-0.16$ and $r=-0.17$) and positively for lateral and total-tibial plateau area ($r=0.18$ and $r=0.16$). Conversely, change in PWC_{170} was positively associated with changes in cartilage volume at all sites ($r=0.24$-0.26). All associations $P<0.05$. Overall, these associations were modest in magnitude but suggest that knee cartilage volume and tibial plateau area are dynamic structures that can respond to physical stimuli. Greater muscle strength and endurance fitness, especially in women, may be protective against cartilage loss, however it may

also result in a maladaptive enlargement of subchondral bone in both sexes, suggesting PA may have both good and bad effects on the knee.

In **Chapter 6**, we report on 1,434 children, aged 7 to 15 years, who had health and fitness measures taken in 1985 and approximately 20 years later (mean age 31). Heel bone mass was also determined at follow-up using a Sahara bone ultrasound densitometer. In females, there were modest but significant beneficial relationships between childhood 1.6 km run, 50 m sprint and standing long jump and adult bone mass. In both sexes, PWC_{170} at age nine years had a greater influence on adult bone mass (R^2 = 5-8%, all $p<0.05$) than it did for 15 year olds (R^2 = <1%, all $p>0.05$) independent of adult performance. In the 12 year olds, childhood PWC_{170} was also associated with female adult bone mass (BUA: R^2 = 6%, $p=0.045$). In males, childhood body mass index (BMI) (but no performance measures) was positively associated with adult bone mass after adjustment for adult BMI. In conclusion, childhood fitness levels, particularly in females and in the early pubertal years, were predictive of adult skeletal status as measured by quantitative ultrasound, while BMI is predictive in males only. These results suggest that increased skeletal loading in childhood leads to an increase in peak bone mass independent of current loading.

Chapter 7 sought to determine if pre-pubertal dual energy x-ray absorptiometry (DXA) could predict fracture risk during puberty. In 183 children who were followed for 8 years (1460 person years) there were a total of 63 fractures (43 upper limb). In unadjusted analysis only total body BMD showed an inverse relationship with upper limb fracture risk ($p=0.03$). However, after adjustment for height, weight, age (all at age 8) and sex, total body BMC (HR/SD 2.47 95% CI 1.52 - 4.02), spine BMC

(HR/SD 1.97 95% CI 1.30 - 2.98), total body BMD (HR/SD 1.67 95% CI 1.18 - 2.36), total body BMAD (HR/SD 1.54 95% CI 1.01, 2.37) and spine BMD (HR/SD 1.53 95% CI 1.10, 2.22) were all significantly associated with upper limb fracture risk. Similar, but weaker trends were present for total fractures. There was a trend for overweight/obesity to be associated with upper limb fracture risk (HR 1.53/category, p=0.08). As such, measurement of bone mass by DXA was a good predictor of upper limb fracture risk during puberty. Although we did not measure true bone density, the constancy of fracture prediction following a single measure suggests bone strength remains relatively constant during puberty despite the large changes in bone size.

Chapter 8 built on the findings on Chapter 7 to describe tracking of dual energy x-ray absorptiometry (DXA) measures from age 8 to age 16-years and whether this was independent of change in body size and whether altered tracking could be predicted. We found all DXA measures tracked significantly after adjustment for change in height and change in weight (males: R^2: BMC 24-62%; aBMD 41-48%; BMAD 30-37%, females: R^2: BMC 45-72%; aBMD 36-56%; BMAD 30-48%). Factors that predicted subjects would *deviate positively,* that is improve in tertile or remain in the highest tertile of spine and hip aBMD included having been breastfed, increase in LM, PWC_{170} at age 8 and sport participation in males. LM at age 8 was beneficial in males while in females; higher FM at age 8 predicted subjects would *deviate positively.* Boys who gained absolute and percent FM and girls who gained percent FM, were more likely to *deviate negatively,* that is, decrease in tertile or remain in the lowest tertile of spine and hip aBMD. Inhaled corticosteroid (ICS) use at age 8 also predicted subjects, particularly males would not improve in bone mass relative to their peers. In conclusion, DXA measures track moderately to strongly from childhood to

adolescence. This was independent of linear growth and sex indicating bone development and physical growth are under largely separate mechanistic control. Body composition was the main predictor of altered tracking but environmental factors also appear important.

In **Chapter 9** we examined the association between pedometer determined ambulatory activity (PAA) and bone mass over 2.6 years in 872 community dwelling males and females, aged 50 – 80 years. At baseline, PAA was positively associated with hip aBMD. An age interaction was present with steps having a stronger association for those aged over 65 years. Longitudinally, the effect of steps on hip aBMD was constant, but not additive over time. For those over 65 years, the difference in hip aBMD between the lowest and highest steps quartile ranged from 3.1% to 9.4%. With regard to the spine, the relationship between daily steps and spine aBMD was modified by sex. For males; there was no significant relationship between steps and spine aBMD. However, for females, higher steps were associated with higher spine aBMD with the effect being constant over time but not additive. There was no evidence of a threshold effect. In conclusion, pedometer determined ambulatory activity has consistent associations with hip aBMD in both sexes which appears most important in those over 65 years of age. The associations for spine aBMD were both weaker and inconsistent suggesting site specificity.

Chapter 10 summarises the findings of the thesis and suggests directions for future research.

CHAPTER 1: EPIDEMIOLOGY OF FALLS, OSTEOARTHRITIS AND OSTEOPOROSIS

Prelude

The studies that make up this thesis are linked broadly but do not necessarily follow sequentially in regard to the pertinent literature. For this reason, a comprehensive review of the literature specific to each research question will be presented at the start of Chapters 4 – 10. In this chapter, the epidemiology of falls, osteoarthritis and osteoporosis will be presented with a brief discussion of the literature specific to individual research questions.

1.1 Population ageing

Population ageing is unprecedented and enduring. The United Nations estimate that the proportion of older persons increased from 8% in 1950 to 10% in 2000, and is projected to reach 21% in 2050 (Figure 1.1) (1). What's more, the older population is itself ageing. Octogenarians are the fastest growing age group. They currently comprise more than one tenth of older persons and are increasing at 3.8% per year, meaning that by 2050, one fifth of older persons will be 80 years or older (1). In Australia, the projections are almost identical. In 2004, the number of Australians aged 65 or more was estimated to be 2.6 million or around 13% of the population (ABS 2005 Population Projections, Australia). This proportion is projected to increase over time to 26% in 2051 and remain at similar levels in 2101 (ABS 2005 series B) (Figure 1.2), or to 28% and 31% respectively (ABS 2005 series C). As the population ages, the prevalence of falls, and chronic diseases that disproportionately affect the elderly will increase markedly. Two such diseases are osteoarthritis and osteoporosis.

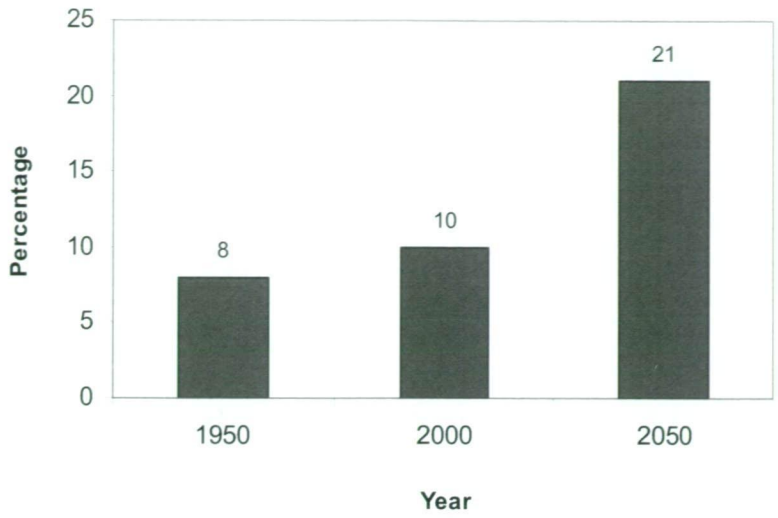

Figure 1.1. Proportion of population 60 years or older: world, 1950-2050. Adapted from United Nations, 2001

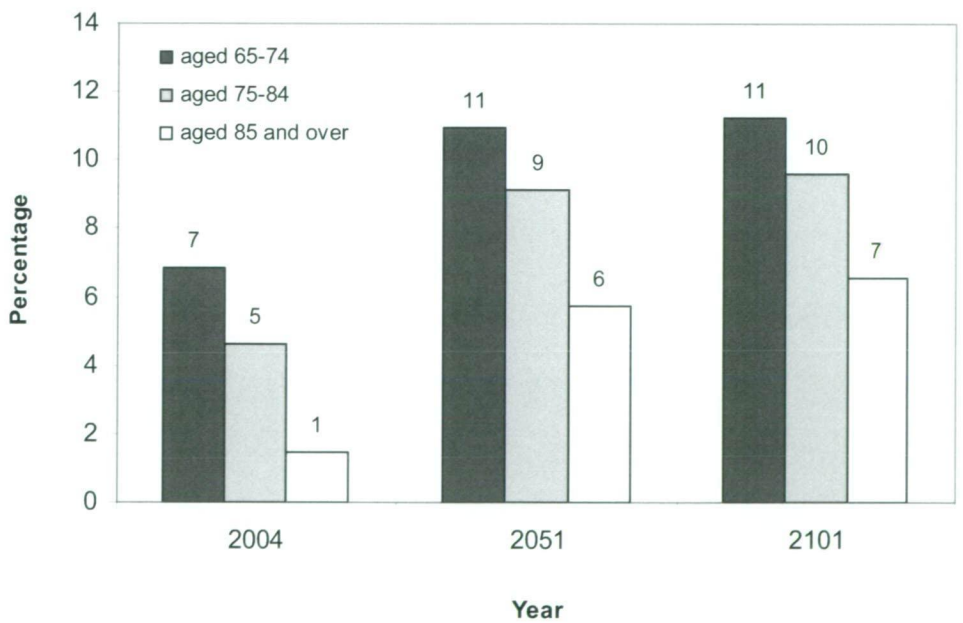

Figure 1.2. Projected population by age: Australia, 2004-2101. Adapted from Australian Bureau of Statistics, Population Projections Series B, Australia, 2004-2101, (3222.0)

The prevalence of falls, OA and osteoporosis increases exponentially from the age of 50 years. 30% of older people experience one or more falls each year (2-4). Similarly, 30% of people aged 65 years and over suffer from osteoarthritis of the knee (5), while one in three women and one in five men over the age of 50 years are affected by osteoporosis (6,7). Therefore the chances of suffering one of these conditions in older age are considerable. Hip fractures, the most serious consequence of osteoporosis have been predicted to rise globally from 1.66 million in 1990 to 6.26 million by 2050 (8). In Australia, the number of hip fractures in women is projected to increase from 11,300 per year in 1996 to 44,700 in 2051 and from 4,000 to 15,300 in men (9).

Population ageing is expected to increase costs of health care in most societies because health expenditure by and for older age groups tends to be proportionally greater than their population share. For example, in Australia where long-term care is inclusive of public health schemes, per capita expenditure for people age 65 and over may be up to four times higher than that for young people. In 2004-05, arthritis and musculoskeletal conditions constituted the third largest component of Australia's health expenditure, after cardiovascular diseases and nervous system disorders, with an estimate of $4.6 billion (10). This equated to 9.2% of allocated health expenditure.

Due to population ageing and the already high prevalence and associated costs, prevention of falls, OA and osteoporosis has been widely recognised as a public health priority. In Australia, 2001-2010 has been labelled the Bone and Joint Decade and musculoskeletal disorders have been recognised as a national health priority with OA and osteoporosis being 2 of the 3 musculoskeletal conditions included in the Arthritis and Musculoskeletal Conditions National Action Plan. The United States has similarly followed suit, declaring 2002-2011 as the Decade of the Bone and Joint.

1.2 FALLS

One of the major problems associated with ageing is the increased susceptibility to falling. Although most falls are considered accidents, the incidence of falls differs from a Poisson distribution (11) indicating they are not random events.

1.2.1 Prevalence and incidence

The term 'prevalence' refers to the estimated population of people who experience the disease at any given time, while the term 'incidence' refers to the annual diagnosis rate, or the number of new cases diagnosed each year.

Retrospective community studies have found about 30% of older people experience one or more falls each year (2-4). Prospective studies have found a slightly higher incidence rate. In the Australian Randwick falls and fracture study, 39% of community dwelling women (mean age 74.6 years) reported one or more falls in a follow-up period of 1 year (12). Similarly, Campbell *et al* (13) found 40% of women and 28% of men aged over 70 years fell at least once in the following year, an overall incidence rate of 35%. Three other studies have reported incident rates of around 30% in people aged over 65 years (14-16). Rates of 2 or more falls average 15% and 3 or more falls, 8% (12). Falling rates also increase beyond the age of 65 years (12). In nursing homes and hospitals, incidence rates of falls and associated injuries are almost three times the rates for community-dwelling persons aged over 65 years (17).

1.2.2 Consequences of falls

Falls are the leading cause of injury-related hospitalisation in persons aged 65 years and over, and account for 4% of all hospital admissions in this age group (18).

In Australia, Lord *et al* (19) showed that with advancing age, the incidence of fall-related hospital admissions increased at an exponential rate. After the age of 40, the admission rate due to falls increased by 4.5% per year for men and by 7.9% per year for women. In those aged over 85 years, 40 per 1000 falls in men and 70 falls per 1000 in women required hospital admissions.

Fall-induced injuries are one of the most common causes of longstanding pain, functional impairment, disability and death in elderly populations (20,21). About 5% of falls result in fracture and 5-10% result in other serious injuries such as severe head injuries, joint dislocations and soft-tissue bruises, contusions and lacerations (22-26). Hip fractures comprise approximately 25% of fractures resulting from falls in the community (27). The age adjusted incidence of fall induced deaths in 1995 was estimated to be around 47 and 38 per 100 000 persons aged over 50 years for men and women respectively (20). Falls are also cited as predictor of nursing home admissions (28).

1.2.3 Cost of falls

Falls constitute a significant health care cost. Englander *et al* (29) estimated the cost of falls in the United States to be $20.2 billion in 1994, with a cost per injured person being $7399. More recently, the direct medical costs of falls in 2002 was estimated to be 7.8 billion, with the cost per injured person being $2591 (30). This later estimate is substantially lower as the direct non-medical, intangible and indirect costs were not included.

1.2.4 Risk factors

A number of falls risk factors have been identified. These can be classified as either intrinsic (lower extremity weakness, poor grip strength, balance disorders, functional and cognitive impairment, visual deficits) or extrinsic (polypharmacy and environmental factors such as poor lighting and loose carpets) (31). Arthritis has also been identified as a possible risk factor for falls and this will be explored further in Chapter 4.

1.3 OSTEOARTHRITIS

Osteoarthritis (OA) is a condition characterised by changes to the integrity of articular cartilage and subchondral bone. It is the most common musculoskeletal disorder affecting Australians, and is the leading cause of disability and pain within the community. The chronic disability and poorer quality of life imposed by osteoarthritis is of great public health importance and a huge concern for society.

1.3.1 Definition

OA can be defined by structural pathology, such as on x-ray, joint symptoms or a combination of the two. Joint pathology is diverse, and includes focal damage and loss of articular cartilage, abnormal remodelling and attrition of subchondral bone, osteophytes, ligamentous laxity, weakening of periarticular muscles, and in some cases, synovial dissention and inflammation. Many patients with radiographic changes consistent with OA are asymptomatic or do not exhibit disability. In those for whom symptoms are present, the primary symptoms include pain, stiffness and limitation of movement of the affected joint.

X-ray is regarded as the gold standard for the diagnosis of osteoarthritis (in combination with pain), however changes apparently occur slowly, possibly due to them being greatly diluted by measurement error. Other drawbacks to plain radiography for the diagnosis and evaluation of OA include radiologic evaluation is relatively insensitive in depicting early changes, articular or other non calcified structures of the affected joint cannot be directly visualised, and although osseous findings are common in OA, they tend to arise late in the disease process. Furthermore, radiography projects a three-dimensional anatomy onto a two-dimensional image, which results in morphological distortion, magnification and superimposition of overlying structures. Lastly and as previously mentioned, there is only a modest association between pathology and symptoms (32-40), though advanced radiological changes, particularly severe osteophytes are more likely to be symptomatic (35).

1.3.2 Prevalence and incidence

In the 2001 National Health Survey (41) about 75 out of 1,000 Australians reported osteoarthritis. This equated to around 1.4 million people. Symptomatic OA was also reported by more than one-quarter of person aged 60 and above in the Dubbo Osteoporosis Study (42). Knee OA is the most frequent with a reported prevalence of 30% in Americans aged 65 years and over (5). Other commonly affected joints include the hips, ankles, hands and feet. The Framingham Osteoarthritis Study, incorporating patient responses to a standardised questionnaire about knee OA, physician assessment and radiographic evidence (Kellgren's and Lawrence's criteria) found a clear relationship between knee OA prevalence and age (5). The overall prevalence of OA increased from 27% in subjects younger than age 70, to 44% in

subjects age 80 year or older. Grade 3-4 knee OA rose from 11.5% in patients aged <70 years to 19.4% in those aged >80 years (5).

In regard to hip OA, prevalence estimates have ranged from 1.2% in Sweden to 8% in Iceland (43). In a Dutch population, hip OA prevalence in women rose from 2.6% at ages 55-59 to 14.8% at ages 75 -79, and in men from, 5.9% to 10.2%.

Radiological prevalence surveys have shown changes of OA being present on x-ray in more than 50% of people over the age of 65 years, and almost universally after 85 years (44,45). However, not all radiological OA (ROA) is associated with clinical symptoms, and not all symptomatic OA is associated with disability.

The incidence is difficult to determine and varies depending on whether radiological or a clinical definition is used. The Framingham study showed among women, there was a mean incidence of 2% per year for knee ROA and 1% per year for symptomatic knee OA, with the overall rate being 1.7 times higher in women than men. The risk of progression was 4% per year. In a study on women 55 years or older, Cooper *et al* (46) found rates of incidence and progression were 2.5% and 3.6% per year, respectively. No prospective studies have been undertaken in Australia, however using software to model epidemiological parameters, Mathers and Penm (47) estimated there to be some 27,000 new cases of ROA in Australia annually. The incidence also increases with age.

1.3.3 Cost and disease burden

OA exerts a large financial burden on society. In 1993-94, the estimated direct medical cost to the Australian healthcare budget attributable to OA was approximately $624 million (10). In 2000-01, this had risen to an estimated $1.2 billion, of which the largest proportion was due to joint replacement surgery. Almost

50% of surgical procedures performed on persons with OA as the principal diagnosis were for total joint arthroplasty (10). OA associated costs represent one-quarter of the total expenditure on arthritis and musculoskeletal conditions and accounted for 1-2.5% of GDP (10).

In Australia, OA is the third largest contributor to life-years lost due to disability, equal to asthma and only exceeded by depression and dementia (48). The loss of quality of life with OA is well documented in population surveys, cohort studies and intervention studies. Specifically, OA has been cited as the most common self-reported cause of restriction in activities of daily living (49). In Europe it was estimated osteoarthritis accounted for 3.1 million lost DALYs (disability adjusted life years), the highest of any musculoskeletal conditions (50).

1.3.4 Treatment of OA

Research on cartilage metabolism and repair has given new hope of drug development in the osteoarthritis realm. Unfortunately, in review of such advances, Fenner (51) reached the conclusion that it was unlikely there would be any new therapies for OA that would have a realistic impact on the disease within the next 10-15 years. As there is no cure, OA management is primarily concerned with controlling the pain and improving function and quality of life. For example, exercise can improve function and reduce pain in people with hip and knee OA (52). Topically applied non-steroidal anti-inflammatory drugs (NSAIDs) have also been shown to be effective (53).

1.3.5 Risk factors for OA

Modifiable risk factors for the development of OA include joint injury, obesity and occupational overuse. Unmodifiable risk factors include age, family history, female sex and race.

1.3.6 Physical activity and OA

This topic will be discussed in detail in Chapter two. Briefly, the relationship between physical activity and osteoarthritis is uncertain. Observational studies have generally suggested a higher risk of radiographic knee OA with high impact sports (54) although studies of recreational activity suggest no risk (55) or a decreased risk (56). Randomised trials in animals have demonstrated that treadmill type exercise decreases the risk of developing OA of the weight bearing joints (57,58). Exercise intervention studies in humans with OA of the knee convincingly show that exercise, virtually regardless of type, improves symptoms (52).

1.4 OSTEOPOROSIS AND FRACTURES

Osteoporosis is a disease in which the density and quality of bone are reduced, leading to weakness of the skeleton and increased risk of fracture. It is often referred to as the 'silent disease' as a fracture is often the first sign.

1.4.1 Definition of osteoporosis

The WHO definition of osteoporosis is a hip bone density T-score at or below 2.5 standard deviations (T score) below normal peak values for young adults. The WHO definition only takes into account measurement of bone density, with no

component of bone quality. As such, the NIH Consensus Development Panel on Osteoporosis developed a clinical definition of osteoporosis. It stated "Osteoporosis is defined as a skeletal disorder characterise by compromised bone strength predisposing a person to an increased risk of fracture". Nevertheless, measurement of bone mineral density (BMD) remains the most useful clinical tool available to diagnosing osteoporosis.

1.4.2 Prevalence and incidence

2.2 million Australians have an osteoporosis related condition, currently affecting 10% of the population. This figure will become 3 million by 2021. 1.65 million are women and 0.51 million are men (59). This is likely to be an underestimation however, given as many as 4 out of 5 people with osteoporosis do not know that they have it (60).

The public health and clinical importance of osteoporosis lies in the fractures associated with the disease. 1 in 3 women aged over 50 will suffer a fracture due to osteoporosis and this fraction increases to 1 in 2 over 60 (6,7). For men, 1 in 5 will suffer a fracture due to osteoporosis increasing to 1 in 3 aged over 60. According to conservative estimates, a 50-year-old Caucasian woman has a remaining lifetime risk of 40% for hip, vertebra or wrist fractures (61). In Australia in 2007, someone was admitted to hospital with an osteoporotic fracture every 5-6 minutes, with an average of 262 hospitalisations per day (59).

In the year 2000 it was estimated 9.0 million osteoporotic fractures occurred worldwide of which 1.6 million were at the hip and 1.4 million were clinical vertebral fractures (50). The annual incidence rate of osteoporotic fractures in women is greater than the combined incidence rates of heart attack, stroke and breast cancer.

1.4.3 Cost and disease burden

Osteoporosis accounted for 5% or $221 million of Australia's total expenditure on musculoskeletal conditions in 2000-01. The greatest proportion was due to pharmaceutical treatments (37%) with prescription medications comprising 97% of this (10). Hip fractures impose the heaviest burden on the community as a result of both acute care and rehabilitation. Indeed, in respect to direct costs, the majority were incurred by hospitalised patients and related hospital and rehabilitation costs. In Australia, around 64,000 hospital separations in 2000-01 were for fractures in people over 55 years of age. Of these, hip fractures constituted 37% and this increased to 55% among those aged 85 and over. The total number of bed days associated with acute care episodes for hip fracture was 244,178 days compared with 160,407 for head injury (10).

Almost half of those who suffer a hip fracture will be permanently disabled and not regain their former independence (62) and up to 80% will have difficulty with daily activities, including walking (63). Approximately 25% of people who sustain a hip fracture die within 12 months of the fracture (64), but these deaths are often attributed to other underlying causes. Many vertebral fractures are occult and asymptomatic, however they are also associated with an increased mortality rate (65). Women who suffer a vertebral fracture are 4 times more likely to sustain a new vertebral fracture within a year (66).

From a global perspective, in the year 2000, 0.83% of the burden of non-communicable diseases was accounted for by osteoporotic fractures. In Europe more DALYs were lost from osteoporotic fractures than common cancers and many other chronic conditions including asthma and hypertensive heart disease. In relation to

musculoskeletal conditions, 2 million DALYs were lost due to osteoporosis, second only to OA (50).

1.4.4 Treatment of osteoporosis

Anti-resorptive drugs reduce the risk of fracture by 50% in women, and probably men, within people with WHO defined osteoporosis (67). Most fractures in absolute numbers however, are derived from a much larger population, that is, people between 1.0 to 2.5 SD below the young normal mean. There have been no trials showing drugs to be effective at reducing fracture risk in people with osteopenia. It would not be considered evidence based approach, nor feasible or cost-effective to treat everyone 50 years and over. Thus we need to use other strategies to prevent and/or reduce the public health burden of fractures. Such strategies must be safe, accessible to all and inexpensive to implement, i.e. exercise.

1.4.5 Risk factors for osteoporosis

Osteoporosis risk factors are by and for the most part, those factors which increase the rate of age-related bone loss and lead to an increased risk of fracture. Like osteoarthritis, risk factors fall into two main categories, fixed and modifiable. Fixed or unmodifiable risk factors include age, female gender, family history, previous fracture, race, menopause/hysterectomy, long term glucocorticoid use and primary/secondary hypogonadism in men. Modifiable risk factors include alcohol consumption, smoking, low BMI, eating disorders, insufficient exercise, low dietary calcium intake and vitamin D insufficiency.

1.4.6 Bone development and changes throughout life

Skeletal growth in the foetus and infant is rapid, but most childhood bone acquisition takes place slowly until puberty, when it becomes rapid again. Bone mass acquisition occurs through skeletal growth or modelling, both longitudinal growth at the growth plate and cross-sectional growth at the periosteum. Bailey *et al* demonstrated that as much bone mineral will be laid down during the adolescent growing years as most people will lose during all of adult life (68). About 85-90% of final adult bone mass is acquired by ages 18 years in girls and 20 in boys (69,70). In a longitudinal study, Martin *et al* (71) showed the highest velocities of bone mineral addition to the skeleton lagged peak height velocity by 1.6 years in girls and 1.2 years in boys. The peak bone mass attained is very important in determining whether an individual is at risk from osteoporosis and subsequent fractures later in life. If it is low, then even small amounts of bone loss may result in fracture whereas, if it is high, an individual may be protected from osteoporosis.

In both men and women, age-related bone loss begins around the age of 40 years and continues throughout life. In women about 35% of cortical bone and 50% of trabecular bone in the skeleton is lost during a lifetime, whereas men lose about two-thirds of this amount (72,73). Cortical bone is lost at a rate of around 0.3-0.5% per year. Type 1 or postmenopausal osteoporosis generally occurs before the age of 65 and affects 5-25% of women in early menopause (72). Oestrogen deficiency is the prime cause for menopausal bone loss in women. Type 2 osteoporosis occurs universally in both men and women after peak bone mass has been attained and involves the loss of both trabecular and cortical bone. Menopause is followed by an immediate decrease in bone mass and density within a year at both peripheral and central sites. Approximately 10 years after menopause, the increased rate of bone loss

reaches equilibrium and then merges into a continuous age-related loss of predominantly cortical bone (74). Importantly, the rate of femoral neck bone loss has been shown to increase with advancing age, indicating an exponential or quadratic decline in absolute bone mineral density (75,76).

We can summarise bone changes throughout life graphically. Figure 1.3 shows why a low adult peak bone mass (red, dashed) and bone mass lost at a faster rate than it should be (black, solid), increases the risk of fracture at an earlier age. The blue dashed line demonstrates how and why achieving an optimal peak bone mass is protective against late-life fragility fractures.

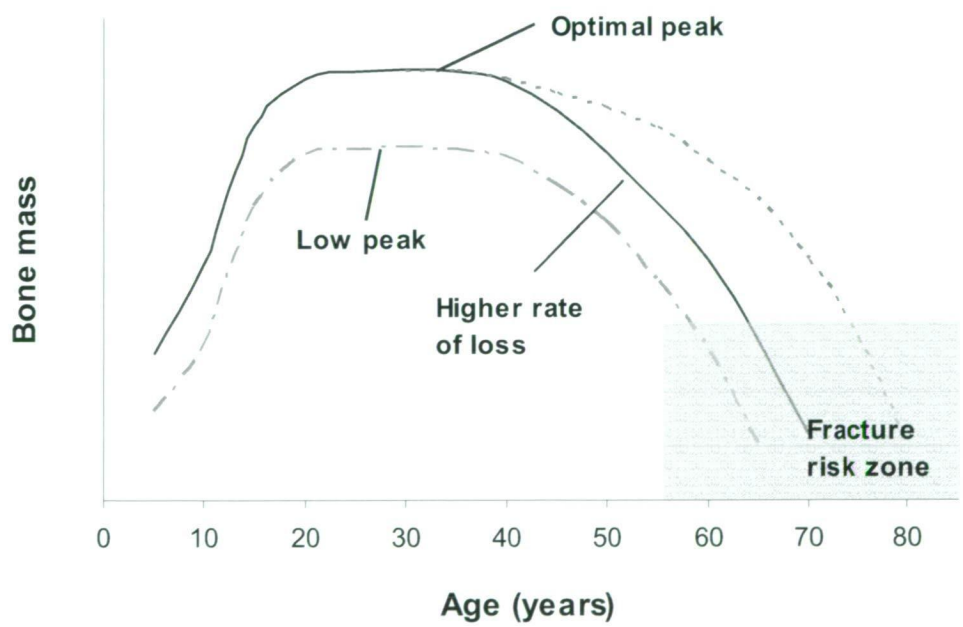

Figure 1.3. Bone mass changes throughout life, showing effect of low peak bone mass, or higher rate of bone loss.

1.4.7 Can physical activity increase peak bone mass?

It is well recognised that physical activity in childhood leads to gains in bone mass, much more so than what is observed in adult training trials. What has not been investigated up until now is whether physical activity leads to higher peak bone mass that is maintained into adulthood. Chapter 6 will address this.

1.4.8 Can physical activity prevent age related bone loss?

Weight bearing activity can maintain bone mass by preventing bone loss. Several training trials have shown high intensity activity can be beneficial (77), while the evidence surrounding walking (78-81), an activity that is preferred by older people, is much less convincing. There have been no prospective studies investigating objectively measured habitual ambulatory activity and changes in bone mass in older people. This will be the topic of Chapter 9.

1.4.9 Childhood fractures

We have described the high prevalence of fractures in the elderly but fracture incidence is bimodal with a peak in adolescence and again in the elderly (82). In fact, childhood fractures outnumber those due to osteoporosis by a factor of three (83). The high incidence in childhood has been thought to be a result of a transient decrease in bone mineralisation relative to bone growth. However evidence now suggests that fractures in childhood are also a result of underlying skeletal fragility. We will explore this topic further in Chapter 7.

1.4.10 Tracking of bone mass

If childhood fractures result from long term skeletal fragility, then this implies bone mass tracks. That is, individuals maintain their position in the distribution curve over time. It is this notion of tracking that will be explored further in Chapter 8.

1.5 Summary

By 2050, the proportion of those aged over 65 would have increased from 13% to 26%. As the population ages, the prevalence of falls, osteoarthritis and osteoporosis, including resulting fractures will increase markedly. These conditions constitute a major health problem due to their large contribution to illness, pain and disability, high frequency and resulting economic burden. Physical activity is an important risk factor risk for falls, osteoarthritis and osteoporosis but many questions remain unanswered. In the following chapters we are going to investigate osteoarthritis as a risk factor for physiological determinants of falls and investigate how PA affects joint structure. We will attempt to answer the question of whether childhood exercise can confer lasting benefits, and explore into the concept of skeletal fragility also being a cause of childhood fractures. Further to this, we'll provide evidence of tracking and explore possible factors that predict deviation from tracking. Lastly, we'll look at an objective measure of physical inactivity and its relationship to bone mass in older age.

CHAPTER 2: RESEARCH QUESTIONS

RESEARCH QUESTIONS

1. What is the relationship between objectively measured falls risk predictors, knee and hip ROA and a measure of pain, stiffness and functional ability in a population-based random sample of 50 – 80 year old, men and women?

2. What is the relationship between strength, endurance fitness, self-reported physical activity and structural change of the knee joint in a convenience sample of adult male and female subjects?

3. What is the relationship between childhood physical performance measures and BMI assessed in 1985 and adult bone mass, as measured by QUS, in a cohort of children who are now young adults?

4. What is the predictive value of a single DXA measurement at age 8 on fracture incidence (including those of the upper limb) between age 8 and 16 years?
   4.1. Do measures of body fat or previous fracture predict subsequent fracture?

5. Does bone mass (BMC, aBMD and BMAD) track from age 8 to age 16 years and is tracking independent of change in body size?
   5.1. What factors predict whether children will change tertiles (either improve or decline) of spine and hip aBMD over the eight year period?

6. What is the cross-sectional and longitudinal association between habitual ambulatory activity assessed by pedometer and bone mass in a community dwelling sample of males and females, aged 50 – 80 years?

CHAPTER 3: METHODOLOGY

Prelude

This thesis has arisen from four different study populations, with a variety of outcome and study factors obtained in each. As such, a detailed methodology pertaining to each study will be given within the Methods section of each chapter.

3.1 Subjects

Four study populations were used in this thesis (Table 3.1). Each population will be described in detail in their relevant chapters.

3.2 Study factors

Study factors for each research question are presented in abbreviated form in Table 3.2. Each study factor will be described in detail in the first chapter they appear.

3.3 Data analysis

Details of statistical analyses will be presented in their relevant chapters. All statistical analyses were performed on either Intercooled Stata versions 8.2, 9.0 or 10.0 for windows (StataCorp LP).

3.4 Ethical issues

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved all the studies, and all participants (or their parents if aged less than 16 years) gave written informed consent.

Table 3.1. Study populations used in this thesis.

Study and chapter	Source and sampling method	Year*	Age †	N
Tasmanian Older Adult Cohort Study (TASOAC) Chapter 4 and 9	Randomly selected from electoral role (equal distribution from urban and rural areas)	2002-08	50-80	P1:1099 P2: 875
Knee Cartilage Volume Study (KVC) Chapter 5	Convenience (adult children of subjects who had had a knee replacement performed for primary knee OA and randomly selected controls from electoral roll).	2000-04	26-61	325
Australian Schools Health and Fitness Survey (ASHFS) Chapter 6	Representative sample of AUS school children (two stage random sampling)	1985	8-15	8,498
Childhood Determinants of Adult Health (CDAH) Chapter 6	Follow-up of ASHFS	2004-06	26-35	2,410
Tasmanian Infant Health Study (TIHS) Chapter 7 and 8	Infants at high risk of SIDS	1988-89	birth	1,411
Blood Pressure and Bone Development Study Chapter 7 and 8	Follow-up of TIHS subjects born in 1988	1996	8	330‡ (444)
T Bone Study Chapter 7 and 8	Follow-up of children who participated in 1996 or 1997 study	2004-06	16	183§ (415)

*Years of data collection †Age at enrolment ‡Number of children who had a DXA scan: Total number of participants in parenthesis. § Number of children who had a DXA scan in 1996: Total number of T Bone participants in parenthesis.

Table 3.2. Research questions and applicable study

Research question	Study	Outcomes*	Main study factors*	Other covariates
1	TASOAC	Falls risk (PPA)	ROA and pain, dysfunction and stiffness (WOMAC)	Age, BMI, RA
2	KCV	CV, BA, cartilage defects (MRI)	PWC_{170}, leg strength and participation in sports	BMI, smoking, knee injury, ROA
3	ASHFS and CDAH	Adult bone mass – BUA, SOS (QUS)	Childhood fitness and BMI	Adult fitness and BMI
5	BP and Bone Development Study and T Bone Study	Upper limb fractures (self-report with x-ray confirmation)	BMC, aBMD, BMAD (DXA)	Height, weight, previous fracture, FM, BMI
4	TIHS, BP and Bone Development Study and T Bone Study	BMC, aBMD, BMAD (DXA)	Breastfeeding, ICS use sports participation (questionnaire), PWC_{170}, LM, FM (DXA)	Height, weight, Tanner stage
6	TASOAC	aBMD (DXA)	PAA (steps/day)	Height, weight, smoking, medication, vitamin D, alcohol and calcium intake

*Method of measurement in parenthesis. PPA: Physiological profile assessment; ROA: radiographic osteoarthritis; BMI: body mass index; RA: rheumatoid arthritis CV: cartilage volume; BA: bone area; MRI: magnetic resonance imaging; PWC_{170}: physical work capacity at 170 beats/min; BUA: broadband ultrasound attenuation; SOS: speed of sound; BMC: bone mineral content; aBMD: areal bone mineral density; BMAD: bone mineral apparent density; DXA: dual energy x-ray absorptiometry; ICS: inhaled corticosteroids; LM: lean mass; FM: fat mass; PAA; pedometer determined ambulatory activity

CHAPTER 4: FALLS RISK IS ASSOCIATED WITH PAIN AND DYSFUNCTION BUT NOT RADIOGRAPHIC OSTEOARTHRITIS IN OLDER ADULTS

4.1 Introduction

One of the major problems associated with aging is the risk of falling, with an estimated 30% of older people living in the community falling one or more times each year (14). Prevention of falls is important as they are one of the main causes of hospitalization and injury related deaths in the elderly (18) and as such, leads to considerable morbidity and suffering for older people. Moreover, falls incur substantial social costs due to hospitalisation and nursing home admissions (31,84).

The notion that osteoarthritis (OA), the most prevalent musculoskeletal disease, increases the risk of falling has been repeatedly stated (13,27,85-87). Indeed, in people with OA, Sturneiks *et al* (87) found 48% had fallen in the previous year compared to 39% of people without OA (sex adjusted relative risk = 1.22). Similarly, Granek *et al* (86) found in elderly nursing home residents, the odds of being a faller rather than a control were significantly higher for those with osteoarthritis. In a community-based prospective study of 761 subjects 70 years and older, arthritis of the knees and increased body sway in men, and muscle weakness in women, were among several factors associated with an increased risk of falling (13). Nevitte *et al* (27) followed 325 community-dwelling persons aged 60 years or older who had fallen during the previous year, weekly for 1 year. They found relatively few predictors of single falls; however there was an increased odds of two or more falls for persons who had arthritis. Conversely, OA has been associated with a decreased risk of any fracture if the diagnosis of OA had been made more than 1 year before the fracture (OR = 0.70, 95% CI 0.67-0.72) (88).

Most of the aforementioned research on OA and falls has relied on self-reported OA, which may be subject to bias. In subjects with OA, pain is the main contributor to disability and is the most common reason for seeking medical

intervention (89). Despite pain having a profound impact on the lives of OA patients, pain and stiffness only occurs in 25 to 50% of patients with radiographic evidence of the disease (5,90). Furthermore, several authors (32-40) have failed to show a strong association between pain scores and radiographic change. For example, of 1004 subjects who reported having knee pain, only 15% had radiographic stage 2-4 changes of OA (39). Summers *et al* (40) found even after controlling for disease severity, psychologic variables remained strong predictors of individual differences in functional impairment and pain. In relation to function, Larsson *et al* (91) reported that a radiographic diagnosis of OA was not related to functional capacity and in turn, Creamer *et al* (92) showed function was determined by pain and obesity rather than by structural changes observed on x-ray. Consequently, when considering OA as a risk factor for falls it may be the symptoms, and not the degree of structural change, that lead to an increased propensity to fall.

Sturnieks *et al* (87) found within people who had self-reported OA, bodily pain was significantly higher in fallers compared to non-fallers. In persons with rheumatoid arthritis, number of pain sites has also been associated with fear of falling (93) and fear of falling can lead to gait changes that further increase falls risk (94). Leveille *et al* (95) followed one thousand elderly women with a disability over 3 years. They categorised pain as widespread pain (pain in the upper and lower extremities and in the axial skeletal region), moderate to severe lower extremity pain (pain that did not meet the criteria for widespread pain) and other pain. In the three groups, knee OA was reported in 50%, 49% and 30% respectively, and by only 13% in the reference group (no or mild pain in one site). Women with widespread pain were seen to have a 60% increased risk of falling during follow-up compared with those who had none or mild pain in only one musculoskeletal site. There was a

significant increase in the risk of falling for women who had foot pain and a non-significant increase associated with any lower extremity pain, and for those who had knee or hip pain specifically. Among women with musculoskeletal pain, risk for falls was also lower in those who used daily analgesic medication. In these analyses however, OA was not adjusted for, despite the high prevalence of OA in this cohort and a significant trend with pain categories. The authors stated that they only included covariates in the model that predicted falls or altered the odds ratio. We can therefore assume that pain was a predictor of falls, independent of self-reported OA. Of note is that the study population was disabled older women, thus these results cannot be generalised to all older women or to older men.

Balance, a fundamental component of falls risk, has also been associated with higher pain scores in patients with severe knee OA and weak knee strength (96). In contrast, in people with stronger knees, pain was not related to balance. Consistent with this, subjects with self-reported OA have worse postural stability and weaker knee extension strength (42,87). Greater body sway was also observed in 11 subjects with knee OA, compared to a similar-age group of healthy adults (97).

Weak quadriceps strength is also a predictor of falls (87) and in turn, pain is associated with muscle weakness (98). In a prospective study, Slemenda *et al* (99) showed reduced quadriceps strength relative to body weight was a predictor of knee OA in women. In patients with OA, knee extension, knee flexion and extension torque has been reported to explain 23-35% of the variation of functional capacity and pain (100). Similarly in patients with OA, Fisher *et al* (101) showed a muscle rehabilitation intervention decreased self-reported pain, dependency and difficulty.

In summary, self-reported OA and bodily pain appear to increase the risk of falling. However there is little data on site-specific radiographic arthritis and falls risk

measures. What is more, the relationship between physiological falls risk predictors and osteoarthritic symptoms have not been examined.

Aim

The aim of this study was to describe the association between objectively measured falls risk predictors, knee and hip ROA and a measure of pain, stiffness and functional ability in a population-based random sample of 50 – 80 year old, men and women.

4.2 Materials and Methods

Subjects

This study was conducted as part of the Tasmania Older Adult Cohort study (TASOAC) an ongoing prospective population based study that began in 2002 (Figure 4.1). Men and women between the ages of 50 and 80 years were randomly selected from the electoral role in Southern Tasmania. Equal distribution was drawn from urban and rural areas. Subjects who were older than 80 years, deceased, too sick, living overseas or interstate, had suffered a stroke, had dementia, had had a hip or knee replacement, weighed more than 135kgs, were institutionalised, had a pace maker or implant, had language problems or suffered from claustrophobia were excluded from the study.The response rate for phase 1 was 57%.

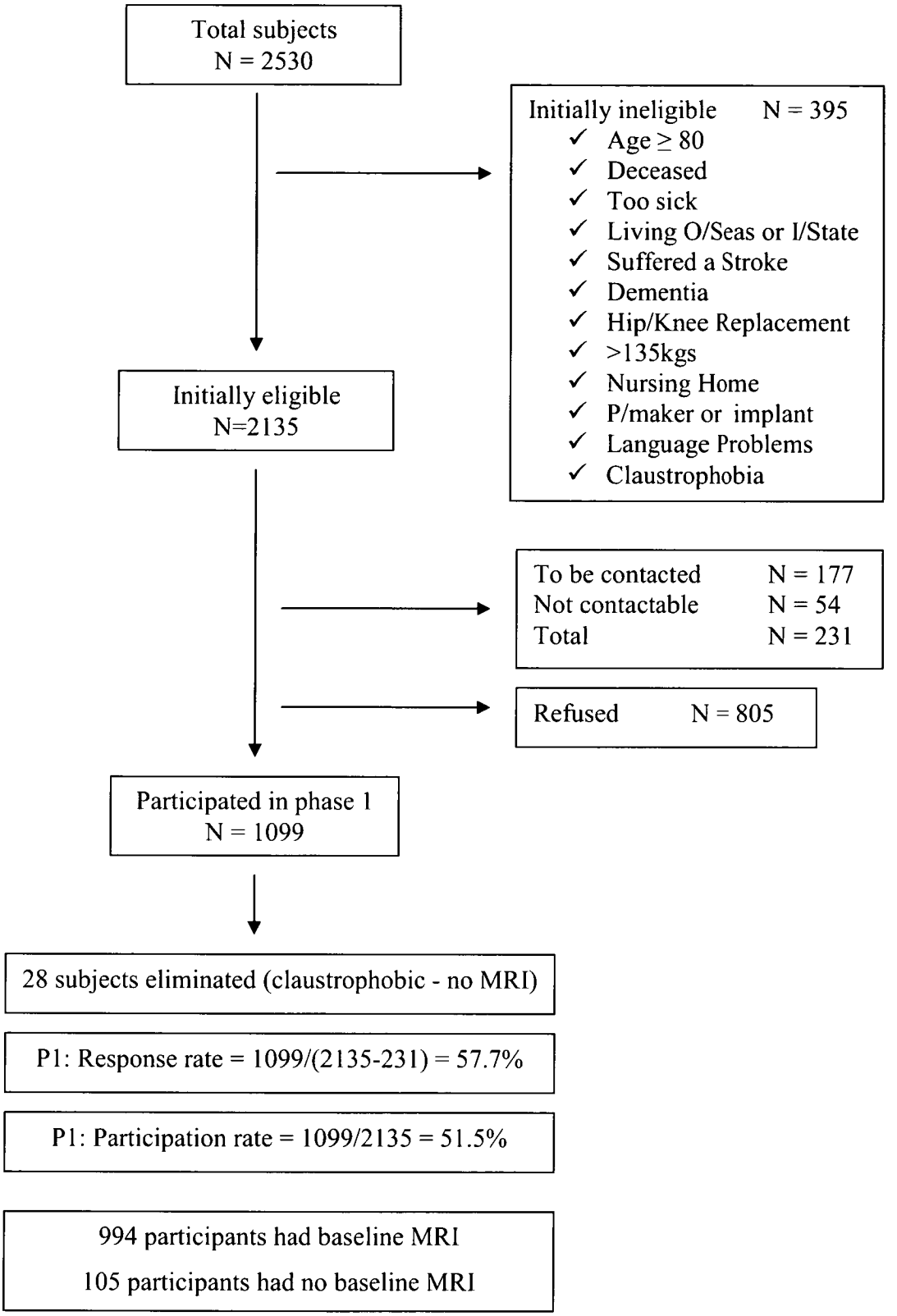

Figure 4.1. Flow chart of TASOAC recruitment and participation

Anthropometrics

Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. Weight was recorded to the nearest 0.1kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) that were calibrated using a known weight prior to each testing session. Body mass index (BMI) was also calculated in kg/m^2 (for weight/height).

Falls risk assessment

The Short Form Physiological Profile Assessment ([PPA] Prince of Wales Medical Research Institute, Sydney, Australia) was used to assess falls risk. This has been described in detail elsewhere (102). Briefly, the short form PPA measures five physiological domains (vision, proprioception, strength, reaction time and balance). Edge contrast sensitivity, an important facet of vision, was measured using the Melbourne Edge Test (103). The lowest contrast patch correctly identified was recorded as the subject's contrast sensitivity in decibel units, where 1 dB=10 $\log_{10}$ contrast. Proprioception was assessed with a lower limb matching task. Subjects were seated with their eyes closed and are asked to align their lower limbs simultaneously on either side of a vertical clear acrylic sheet (60x60x1 cm) inscribed with a protractor and placed between their legs. Any difference in aligning the lower limbs (indicated by differences in matching the great toes on either side of the acrylic sheet) was measured in degrees. After 2 practice trials, an average of 5 experimental trials was recorded. Testing of the knee extensor and flexor muscles was performed using a spring gauge attached to the subject's leg using a webbing strap with a Velcro fastener. The force of the knee extensor and flexor muscles was measured with the subject sitting in a tall chair with a strap around the leg 10 cm above the ankle joint,

and the hip and knee joint angles positioned at 90 degrees. In 3 trials per muscle group, the subject attempted to pull against the strap assembly with maximal force for 2 to 3 seconds, and the greatest force for each muscle group was recorded. Reaction time was assessed in milliseconds using a hand-held electronic timer and a light as the stimulus and depression of a switch by the finger as the responses. The timer has a built-in variable delay of 1 to 5 seconds. Five practice trials were undertaken, followed by 10 experimental trials. Postural sway was measured using a sway meter that measured displacements of the body at waist level. The device consisted of a 40-cm-long rod with a vertically mounted pen at its end. The rod is attached to the subject by a firm belt and extends posteriorly. As the subject attempted to stand as still as possible for 30 seconds, the pen records the subject's sway on a sheet of millimeter graph paper fastened to the top of an adjustable-height table. Testing was performed, with eyes open and closed, on a medium-density foam rubber mat (15 cm thick). One trial of each condition was performed. Total sway (number of square millimeter squares traversed by the pen) and anteroposterior and mediolateral sway were recorded for the 2 tests.

The PPA is a reliable and valid tool for assessing falls risk in older people. Based on the results of five physiological domains, the PPA uses a discriminant function to compute a fall risk score (standardized score) for each individual. This measure has a 75% predictive accuracy for falls in older people (104,105). Falls risk scores below zero indicate a low risk, scores between 0 and 1 a mild risk, scores between 1 and 2 a moderate risk, and scores above 2 indicate a high risk of falling.

Knee pain, stiffness and functional ability

Pain, stiffness and functional ability were assessed by self-administered questionnaire using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (106). The WOMAC is a widely used measure of symptoms and physical disability originally developed for people with osteoarthritis (OA) of the hip and/or knee. Each dimension (pain, stiffness and functional disability) was assessed separately with a 10-point scale, ranging from 0 (none) to 9 (most severe). Each score was then summed to create a total score for each sub-scale (pain: range 0-45, stiffness: range 0-18, functional ability: 0-153). In addition, all three dimensions were summed to give a global WOMAC score (range 0-216). The reliability, validity, and responsiveness of the pain and function subscales of the WOMAC have been demonstrated in a range of patient groups and interventions (107). The questionnaire was self-administered and takes 5 to 10 minutes to complete.

X-ray

A standing anteroposterior (AP) semi-flexed view of both knees was performed in all subjects. Radiographs were then assessed utilising the Altman atlas (108). Each of the following was assessed on a scale of 0-3: medial joint space narrowing (JSN), lateral JSN, medial femoral osteophytes, medial tibial osteophytes, lateral femoral osteophytes and lateral tibial osteophytes. Each score was arrived at by consensus with two readers (VS, HC) simultaneously assessing the radiograph with immediate reference to the atlas. Intra-observer repeatability was assessed in 40 subjects with intra-class correlations (ICC) of 0.65 – 0.85.

Weight bearing AP pelvic radiographs with both feet in 10^{o} internal rotation were obtained and then assessed in the same manner, using a 0-3 scale where 0 = no

disease and 3 = most severe disease. Features assessed included axial JSN, superior JSN and osteophytes. Each score was arrived at by two readers (VS, HC) simultaneously assessing the radiographs with immediate reference to the atlas. Intra-observer repeatability was assessed in 40 subjects with ICC's of 0.60 – 0.87.

Rheumatoid arthritis (RA) was ascertained by the following question "have you ever been diagnosed with rheumatoid arthritis?"

Data analysis

The data were modelling using linear regression. Univariable methods were utilised initially to examine associations with falls risk measures and WOMAC sub-scales, in addition to ROA. Results were then adjusted for sex, age, BMI, ROA and RA where appropriate. The subgroup analyses were adjusted for the WOMAC sub-scales, although pain, stiffness and function were adjusted for ROA only due to co-linearity between the WOMAC sub-scales. A model was constructed containing the WOMAC global score, knee and hip ROA and their interaction term (WOMAC x knee ROA and WOMAC x hip ROA). Statistical significance was determined based on the P value for the interaction term. All results were adjusted for age and sex. Comparison of means between groups was conducted with analysis of variance and post hoc Scheffe analyses. A *p*-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 8.2 for windows (StataCorp LP).

4.3 Results

A total of 850 subjects (male: 424, female: 426) with a mean age of 63 years were included in this study. 249 subjects did not contribute data to these analyses due

to unusable x-rays. Table 4.1 presents the characteristics of the study population. Knee JSN (males: 65%, females: 69%) and hip JSN (males: 34%, females: 40%) was common in both sexes. Self-reported rheumatoid arthritis (RA) was present in just over 10% of the population. Overall, the study population was at mild risk of falling, with mean z scores of 0.09 (SD 0.79) for males and 0.27 (SD 0.27) for females.

Table 4.1. Characteristics of the study population

	Males (n = 424)	Females (n = 426)
Age (years)	63.0 (7.5)	62.0 (7.3)
Height (cm)	174 (6.3)	161 (6.1)
Weight (kg)	84 (13.1)	72 (14.4)
BMI (kg/m^2)	27.8 (3.9)	28.0 (5.5)
WOMAC (global score)	15.7 (26.9)	18.1 (32.0)
Any knee JSN (%)*	65	69
Any knee osteophytes (%)*	14	14
Total knee ROA score (range 0–29)	2.6 (3.3)	2.8 (3.5)
Any hip JSN (%)*	34	40
Any hip osteophytes (%)*	20	18
Total hip ROA score (range 0–36)	1.5 (2.4)	1.7 (2.8)
Rheumatoid arthritis (%)†	10	11
Falls risk (z-score)	0.09 (0.79)	0.27 (0.87)
Edge contrast sensitivity (dB)	20.3 (2.2)	20.7 (2.2)
Reaction time (msec)	229 (38.3)	243 (46.7)
Proprioception (degrees)	2.8 (1.3)	2.7 (1.3)
Knee extension strength (kg)	36.6 (9.6)	23.7 (8.5)
Balance: Eyes open (mm)	48.5 (17.6)	50.1 (18.4)

BMI: body mass index; ROA: radiographic osteoarthritis; JSN: joint space narrowing. The results are reported as percentage for binary variables, and the mean (standard deviation) for continuous variables. *Defined as grade ≥1. †Defined as self-reported rheumatoid arthritis. *Note:* High scores in the reaction time, proprioception and balance tests, and low scores for the contrast sensitivity and knee extension strength tests indicate impaired performances.

Table 4.2, Table 4.3 and Figure 4.2 document the univariable and multivariable associations with falls risk (z score) for WOMAC subscales and ROA. In univariable analysis for males (Table 4.2), age and BMI were significantly associated with falls risk. After adjustment for confounders, only the total pain and function scores were significantly associated with falls risk. When the analysis was stratified by age, a significant association was present between falls risk score and WOMAC function score in younger males (50 – 60 yr olds). After adjustment for ROA and RA, the association between age and falls risk was the only significant association to remain for males. In contrast, in females (Table 4.3), age, WOMAC global score, pain, stiffness, functional ability, knee ROA and hip JSN were all significantly associated with falls risk in univariable analysis. After adjusting for age, BMI and the presence of rheumatoid arthritis, the three WOMAC subscales remained independently associated with falls risk and explained 13-17% of the variation in falls risk, whereas knee ROA and hip JSN were not significantly associated with falls risk. Figure 4.2 illustrates that females who reported a WOMAC score $\geq$50 were more than three times as likely to fall than those below this cut-point ($p<0.001$), while males had a "dose response" association between falls risk and WOMAC score ($p<0.001$ for trend).

Table 4.2. Relationship between study factors and falls risk: Z score for males*

	Univariable analysis	Step 1†	Step 2‡
	β (95% CI)	β (95% CI)	β (95% CI)
Age (yr)	**0.03 (0.02, 0.04)**	**0.03 (0.02, 0.04)**	**0.03 (0.02, 0.04)**
BMI (kg/m^2)	**-0.02 (-0.04, -0.003)**	**-0.02 (-0.04, -0.003)**	-0.01 (-0.03, 0.01)
WOMAC	0.002 (-0.0002, 0.005)	**0.004 (0.001, 0.006)**	0.002 (-0.001, 0.005)
WOMAC sub-scales			
Pain	0.01 (-0.003, 0.02)	**0.02 (0.004, 0.03)**	0.01 (-0.004, 0.02)
Stiffness	0.01 (-0.02, 0.04)	0.02 (-0.003, 0.05)	0.01 (-0.02, 0.04)
Function	0.004 (-0.00004, 0.01)	**0.005 (0.001, 0.008)**	0.003 (-0.001, 0.007)
Knee JSN	0.02 (-0.01, 0.05)	0.01 (-0.03, 0.04)	0.01 (-0.03, 0.05)
Knee osteophytes	-0.02 (-0.06, 0.03)	-0.02 (-0.07, 0.02)	-0.03 (-0.08, 0.03)
Hip JSN	0.04 (-0.004, 0.09)	0.02 (-0.02, 0.07)	0.02 (-0.03, 0.07)
Hip osteophytes	0.01 (-0.04, 0.06)	0.01 (-0.04, 0.06)	0.01 (-0.05, 0.06)

BMI: body mass index; JSN: joint space narrowing. *Linear regression model was used. The results are reported as regression coefficients (β) (95% confidence intervals). †Adjusted for age and BMI. ‡Further adjusted for ROA and rheumatoid arthritis. Bold denotes a statistically significant result.

Table 4.3. Relationship between study factors and falls risk: Z score for females*

	Univariable analysis	Step 1†	Step 2‡
	β (95% CI)	β (95% CI)	β (95% CI)
Age (yr)	**0.04 (0.03, 0.05)**	**0.04 (0.03, 0.05)**	**0.04 (0.03, 0.05)**
BMI (kg/m^2)	-0.002 (-0.02, 0.01)	-0.002 (-0.02, 0.01)	-0.003 (-0.02, 0.01)
WOMAC	**0.008 (0.005, 0.01)**	**0.007 (0.005, 0.009)**	**0.006 (0.004, 0.009)**
WOMAC sub-scales			
Pain	**0.03 (0.02, 0.04)**	**0.03 (0.02, 0.04)**	**0.03 (0.01, 0.04)**
Stiffness	**0.05 (0.03, 0.08)**	**0.04 (0.02, 0.07)**	**0.04 (0.01, 0.07)**
Function	**0.010 (0.008, 0.014)**	**0.010 (0.007, 0.013)**	**0.009 (0.006, 0.013)**
Knee JSN	**0.05 (0.01, 0.09)**	0.02 (-0.02, 0.06)	0.01 (-0.03, 0.06)
Knee osteophytes	**0.04 (0.001, 0.08)**	0.02 (-0.02, 0.06)	0.01 (-0.04, 0.05)
Hip JSN	**0.04 (-0.004, 0.08)**	0.02 (-0.03, 0.06)	0.01 (-0.03, 0.06)
Hip osteophytes	0.01 (-0.05, 0.07)	0.003 (-0.05, 0.06)	0.0004 (-0.06, 0.06)

BMI: body mass index; JSN: joint space narrowing. *Linear regression model was used. The results are reported as regression coefficients (β) (95% confidence intervals). †Adjusted for age and BMI. ‡Further adjusted for ROA and rheumatoid arthritis. Bold denotes a statistically significant result.

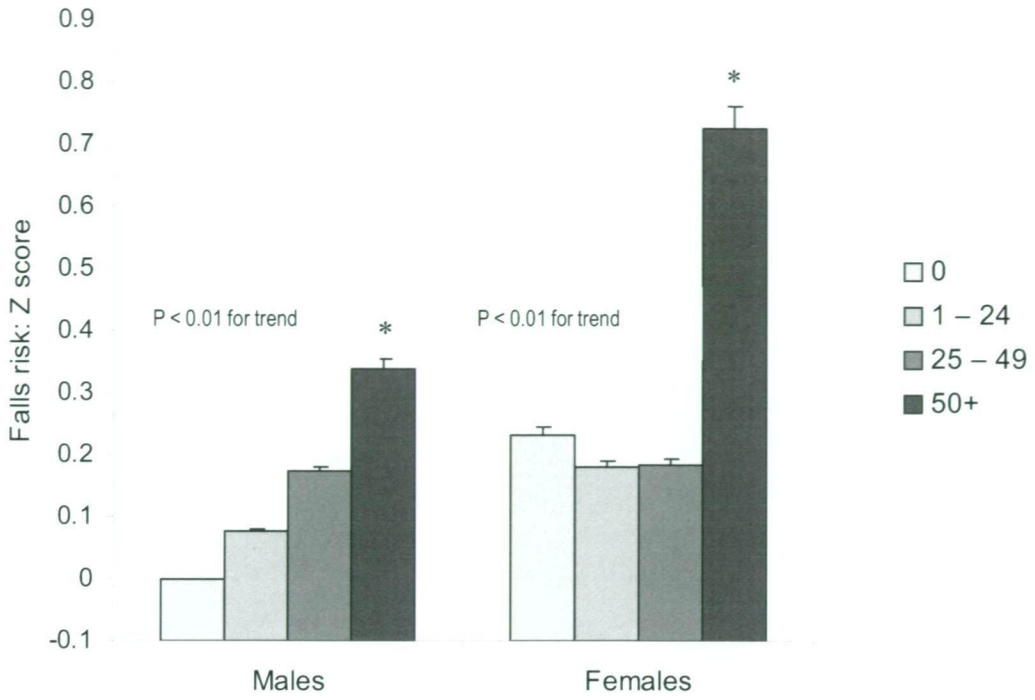

Figure 4.2. The associations between falls risk: Z score and global WOMAC score for males and females. *P* for trend was adjusted for age and BMI. Results are plotted as mean ± S.E.M. * = $P<0.05$ in comparison with the 0 (no pain, stiffness & functional ability) group. ** = $P<0.01$ in comparison with the 0 (no pain, stiffness & functional ability) group. In males there is a dose response while in females there appears to be a threshold of 50.

Table 4.4 displays the univariable and multivariable associations between the WOMAC sub-scales, radiographic measures and the five falls risk components. When adjusted for sex, age and BMI, pain, stiffness and functional ability were significantly associated with all five components, with the exception of stiffness and proprioception. The only significant association for ROA was between hip JSN and knee extension strength. The results differed only slightly when the WOMAC sub-scales and ROA were added to the model. In step 2 of the multivariable analysis, the pain and function scores were significantly associated with all five of the PPA domains. Stiffness was significantly associated with edge contrast sensitivity and knee extension strength. In addition, the relationship between hip JSN and knee extension strength remained significant (p=0.003). Figure 4.3 documents the relationships between each of the five falls risk components and the global WOMAC score.

The knee and hip ROA-WOMAC interaction terms were not significant after adjustment for age and sex (knee: p=0.09; hip: p=0.72). A third interaction term containing both knee and hip ROA by WOMAC was also not significant (p=0.24). When subjects with rheumatoid arthritis (RA) were excluded from the analysis, the results remained largely unchanged. Noted differences from the results presented include, a significant association between the total WOMAC score and function sub-scale, and falls risk for males in multivariable analysis (both p=0.04), with the relationship between pain and stiffness, and falls risk for females becoming non-significant (p=0.13 and p=0.37 respectively). Likewise, in subjects without self-reported RA, pain and stiffness was not associated with balance in univariable or multivariable analysis.

Table 4.4. Relationship between study factors and individual physiological falls risk components*

	Univariable analysis	Step 1†	Step 2‡
	β (95% CI)	β (95% CI)	β (95% CI)
	A. Edge contrast sensitivity (dB)		
Pain	**-0.03 (-0.05 -0.01)**	**-0.03 (-0.05 -0.01)**	**-0.02 (-0.05, -0.001)**
Stiffness	**-0.07 (-0.11 -0.02)**	**-0.07 (-0.11 -0.02)**	**-0.06 (-0.12, -0.01)**
Function	**-0.012 (-0.018 -0.006)**	**-0.012 (-0.018, -0.006)**	**-0.011 (-0.02, -0.005)**
Knee JSN	**-0.09 (-0.16, -0.03)**	-0.06 (-0.12, 0.01)	-0.06 (-0.13, 0.02)
Knee osteophytes	-0.06 (-0.14, 0.01)	-0.04 (-0.11, 0.04)	-0.01 (-0.10, 0.08)
Hip JSN	-0.06 (-0.14, 0.02)	-0.03 (-0.11, 0.05)	0.01 (-0.08, 0.10)
Hip osteophytes	-0.02 (-0.12, 0.08)	-0.02 (-0.11, 0.08)	-0.02 (-0.13, 0.08)
	B. Reaction time (msec)		
Pain	**1.20 (0.79, 1.61)**	**1.18 (0.77, 1.59)**	**0.62 (0.18, 1.06)**
Stiffness	**2.01 (1.07, 2.95)**	**1.93 (0.99, 2.87)**	0.84 (-0.20, 1.88)
Function	**0.41 (0.29, 0.53)**	**0.39 (0.27, 0.51)**	**0.21 (0.07, 0.35)**
Knee JSN	0.77 (-0.60, 2.14)	0.06 (-1.31, 1.42)	-0.73 (-2.28, 0.83)
Knee osteophytes	0.61 (-0.98, 2.20)	-0.17 (-1.77, 1.42)	-0.15 (-2.31, 2.01)
Hip JSN	**2.52 (0.84, 4.19)**	1.53 (-0.14, 3.20)	0.99 (-0.80, 2.78)
Hip osteophytes	-0.10 (-2.20, 1.99)	-0.15 (-2.19, 1.90)	-0.15 (-2.31, 2.01)
	C. Proprioception (degrees)		
Pain	**0.02 (0.01, 0.03)**	**0.02 (0.01, 0.03)**	**0.03 (0.01, 0.04)**
Stiffness	0.02 (-0.01, 0.05)	0.02 (-0.004, 0.05)	0.03 (-0.01, 0.06)
Function	**0.006 (0.002, 0.009)**	**0.006 (0.002, 0.010)**	**0.007 (0.003, 0.011)**
Knee JSN	-0.02 (-0.06, 0.02)	-0.03 (-0.07, 0.01)	-0.05 (-0.09, 0.001)
Knee osteophytes	0.01 (-0.03, 0.06)	0.01 (-0.04, 0.05)	-0.001 (-0.06, 0.05)
Hip JSN	0.03 (-0.01, 0.08)	0.03 (-0.02, 0.08)	0.02 (-0.03, 0.08)
Hip osteophytes	0.004 (-0.06, 0.06)	0.003 (-0.06, 0.06)	0.001 (-0.06, 0.06)

Table 4.4 continued. Relationship between study factors and physiological falls risk predictors*

	D. Knee extension strength (kg)		
Pain	**-0.28 (-0.38, -0.18)**	**-0.27 (-0.35, -0.19)**	**-0.22 (-0.31, -0.13)**
Stiffness	**-0.69 (-0.93, -0.46)**	**-0.69 (-0.87, -0.51)**	**-0.67 (-0.88, -0.47)**
Function	**-0.11 (-0.14, -0.08)**	**-0.10 (-0.12, -0.08)**	**-0.09 (-0.11, -0.06)**
Knee JSN	**-0.71 (-1.04, -.373)**	**-0.45 (-0.72, -0.19)**	-0.28 (-0.58, 0.01)
Knee osteophytes	**-0.41 (-0.80, -0.02)**	-0.13 (-0.44, 0.18)	0.27 (-0.08, 0.62)
Hip JSN	**-1.17 (-1.60, -0.74)**	**-0.62 (-0.96, -0.28)**	**-0.54 (-0.90, -0.19)**
Hip osteophytes	0.01 (-0.51, 0.54)	0.03 (-0.38, 0.43)	0.26 (-0.15, 0.68)
	E. Balance (eyes open) (mm)		
Pain	**0.22 (0.05, 0.39)**	**0.25 (0.08, 0.41)**	**0.20 (0.01, 0.38)**
Stiffness	0.37 (-0.01, 0.75)	**0.42 (0.04, 0.79)**	0.29 (-0.14, 0.72)
Function	**0.12 (0.07, 0.17)**	**0.12 (0.07, 0.17)**	**0.10 (0.05, 0.16)**
Knee JSN	0.54 (-0.01, 1.09)	0.16 (-0.38, 0.70)	0.21 (-0.42, 0.83)
Knee osteophytes	0.29 (-0.35, 0.93)	-0.002 (-0.64, 0.63)	-0.14 (-0.88, 0.61)
Hip JSN	0.60 (-0.08, 1.29)	0.21 (-0.46, 0.88)	-0.19 (-0.91, 0.53)
Hip osteophytes	0.34 (-0.51, 1.20)	0.30 (-0.52, 1.13)	0.51 (-0.35, 1.38)

JSN: joint space narrowing. *Linear regression model was used. The results are reported as regression coefficients (β) (95% confidence intervals). †Adjusted for sex, age and BMI ‡Further adjusted for other factors in table (Pain, stiffness and function were further adjusted for ROA only). Bold denotes a statistically significant result. In multivariable analysis (step 2) sex was significantly associated with A, B and D. Age was significantly associated with A, B, D and E. BMI was significantly associated with D and E.

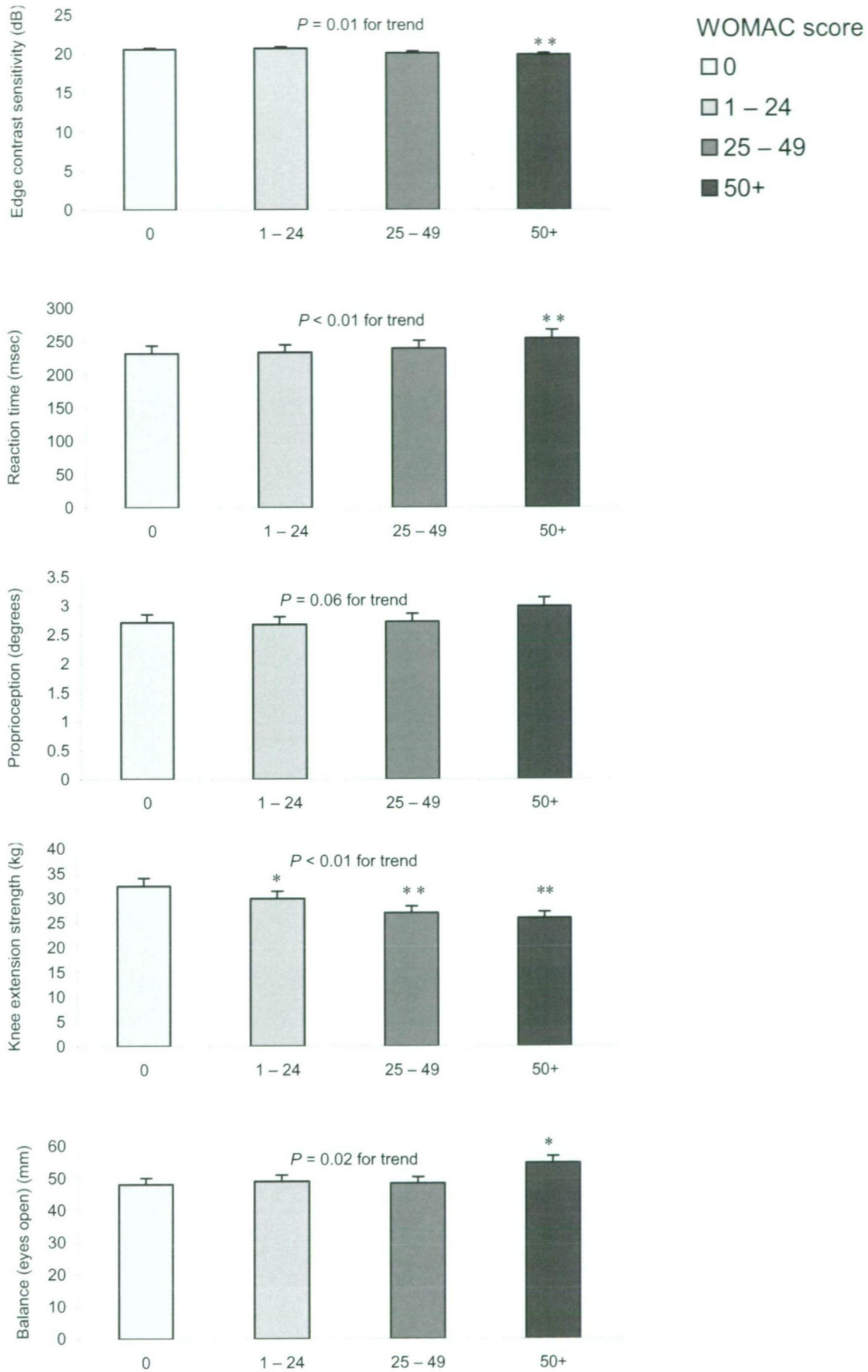
WOMAC score
0
1 – 24
25 – 49
50+
Edge contrast sensitivity (dB)
P = 0.01 for trend
Reaction time (msec)
P < 0.01 for trend
Proprioception (degrees)
P = 0.06 for trend
Knee extension strength (kg)
P < 0.01 for trend
Balance (eyes open) (mm)
P = 0.02 for trend
0
1 – 24
25 – 49
50+

Figure 4.3

Figure 4.3. The associations for global WOMAC score with falls risk measures. *P* for trend was adjusted for age, sex and BMI. Results are plotted as mean ± S.E.M. * = $P<0.05$ in comparison with the 0 (no pain, stiffness & functional ability) group. ** = $P<0.01$ in comparison with the 0 (no pain, stiffness & functional ability) group. There is a modest but significant dose response between total pain, stiffness and functional ability and each falls risk measure with the exception of proprioception.

4.4 Discussion

This cross-sectional study documents that it is self-reported functional ability and pain, and to a lesser extent, stiffness but not radiographic OA, that are modestly but significantly associated with falls risk in community living subjects. Females who reported a WOMAC score ≥50 had more than a three-fold increase in fall risk score compared with women with WOMAC scores below this level. Males also demonstrated a "dose response" association between WOMAC score and falls risk. Consistent results were observed for most of the WOMAC and falls risk subscales with the exception of proprioception.

Although hip JSN was associated with weak knee extensors, no other significant associations were observed between ROA and falls risk predictors. This appears to contradict previous research, which suggests self-reported OA is associated with an increased risk of falling. However, it appears likely that self-reported arthritis reflects pain and dysfunction in older subjects, and our results suggests that pain and dysfunction, rather than radiographic change, increase the propensity to fall. This hypothesis agrees with the observation that pain and disability are the main reasons for persons with OA seeking medical attention (89) and is consistent with a study, in which widespread pain was associated with an increased relative risk of falling (95).

It has been suggested that the WOMAC lacks factorial validity due to the overlap of activities on the pain and function sub-scales (109). In the current study, it appears probable that the function component captured more information than the pain scale alone. Even though in concept, and if measured separately, both pain and function are independently associated with falls risk. As pain is strongly associated with difficulty performing daily tasks (110), it could be speculated that the

relationship between functional ability and falls risk may be mediated by pain. This is supported by a recent paper which suggested that pain was the main contributor to hand dysfunction (111).

There was a modest but significant dose response association between the WOMAC score and the falls risk predictors, with the exception of proprioception. Subjects with more knee pain, stiffness and functional deficit had poorer knee extension strength compared to subjects with a lower OA index score. In the final model, the association between the WOMAC sub-scales and knee extension strength was attenuated by adjustment for hip JSN, with knee JSN making little contribution. In a recent report, the alleviation of knee pain resulted in an increased maximum voluntary contraction (112). A reflex muscle inhibition has been proposed as an intermediate factor on the pathway from pain to muscle weakness (113) and may also explain the association with reaction time. As such, protective balance responses may be impaired by chronic pain and dysfunction, leading to an increased risk of falling.

The observation that pain, stiffness and functional ability are associated with falls risk predictors is important for a number of reasons. In our sample, pain was highly correlated with function and stiffness ($r = 0.81 - 0.86$) and has previously been shown to be associated with difficulty performing daily tasks (110). It would therefore, be expected that pain alleviation would lead to improved functional ability and reduced stiffness. For that reason, encouraging appropriate pain control in the elderly may be one means to lessen the risk of falls. On the contrary, pain can be protective, in that reducing knee pain leads to increased loading of the degenerative portion of the joint (114-116), which may accelerate progression of the disease, although this is yet to be proven. Further studies are needed however, to determine the validity of pain control as a falls prevention strategy. Secondly, pain is not highly

correlated with ROA. Thus, while it is commonly thought that arthritis increases the risk of falling, there are people with arthritic symptoms but no radiographic evidence of the disease, who are likely to be at higher risk of falling. It is therefore, important to treat underlying physiological processes, such as muscle atrophy that accompany symptoms like pain and functional decline.

The current study has a number of potential limitations. The study population was at a mild risk of falling. It is possible that the strength of associations between study factors and falls risk may be different in those at substantially higher risk of falling. Retrospective data on actual falls and fall related injuries was not collected, thus we cannot be certain that identical relationships would exist if such end points were included in the model. However, unlike questionnaires, the PPA is not subject to recall bias, and can predict those at risk of falling with 75% accuracy when the physiological measurements are combined in multivariate discriminate analysis (105). Furthermore, preventing a fall before it actually occurs is the key outcome in falls research, thus the associations noted in regard to physiological predictors will add an important dimension to our understanding of falls prevention. Secondly, the reproducibility of x-ray reading was good rather than excellent, which may weaken associations. Thirdly, the response rate was reasonable at 57%. This does leave the possibility open for selection bias, which may be a reason for the high rates of ROA and rheumatoid arthritis in this cohort. However, this is unlikely to bias the associations we report due to the method of analyses. Likewise, due to multiple comparisons, there is a risk of attaining significance by chance. Therefore, all analysis performed are presented in the current paper. Lastly, as this study was cross-sectional, the causality of relationships cannot be ascertained.

In conclusion, self reported functional ability and pain, and to a lesser extent stiffness (but not knee and hip ROA), have a modest but independent association with physiological predictors of falls risk. Preliminary evidence suggests that the WOMAC may be used as part of a multi-dimensional strategy to identify those at risk of falling. Furthermore, the alleviation of musculoskeletal symptoms may lessen the risk of falls in older people.

CHAPTER 5: PHYSICAL ACTIVITY AND KNEE STRUCTURAL CHANGE: A LONGITUDINAL STUDY USING MRI

5.1 Introduction

Osteoarthritis (OA) is a condition characterised by changes to the integrity of articular cartilage and subchondral bone. The knee is the most frequently affected joint with a prevalence of 30% in people aged 65 years and over (5). Although exercise therapy is effective in improving symptoms of knee OA (52), the relationship between physical activity and structural change of the knee remains unclear.

Randomised trials in animals have shown that both immobilisation and excessive loading can compromise cartilage and subchondral bone. One of the earliest such trials was reported by Radin *et al* (117). They subjected rabbit knees to 1 1/2 the animal's body weight 40 times a minute for 20-40 minutes per day and found subchondral bone stiffening occurred, which was associated with early metabolic changes of cartilage damage. When bone stiffness returned to normal the effect on the cartilage did not completely disappear, though the effects were diminished. Aroskoski *et al* (118) and Lammi *et al* (119) demonstrated that dogs running 40 km/day on a slight incline for 1 year displayed local softening of the articular cartilage and decrease proteoglycan. However they questioned whether these modifications led to OA or if they were only a physiological adaptation to the increase in mechanical constraints. Even so, in dogs subjected to strenuous running of 20 km/day, changes consistent with early cartilage degeneration has been observed (120). Contrary to these findings, moderate running has been seen to enhance proteoglycan content and cartilage thickness of the weight-bearing joints in dogs (57,121) and hamsters (58). Lapvetalainen *et al* (122) also found lifelong voluntary wheel running had a protective effect against OA in mice.

Observational studies in humans have suggested a higher risk of radiographic knee OA with repetitive, high impact sports and this increased risk is most strongly

associated with joint injury (123). Kujala, Kaprio and Sarna (124) compared the cumulative 21 year incidence of hospital admission for OA (hip, knee, and ankle) in 2049 former elite athletes and 1403 control subjects.They divided the cohort into endurance (long distance running, cross-country skiing), team (soccer, ice hockey, basketball, track, and field), and power (boxing, wrestling, weightlifting, throwing) sports. All athletes had higher incidences of admission to hospital for OA than controls, but in endurance athletes the admissions were at an older age. A subsequent study on 117 of these athletes showed the prevalence of knee radiograhic osteoarthritis (ROA) for long distance running, soccer, weightlifting, and shooting were 14%, 29%, 31%, and 3% respectively (125). The prevalence in soccer players was attributed to joint injury, and in weight-lifters - their high BMI. Elite soccer players have been extensively studied with a number of reports suggesting an increased risk from this sport (125-132). A Swedish retrospective cohort reported both hip and knee ROA associations in 71 elite and 215 non-elite players with a mean age of 55 and compared the rates with those of 572 age matched controls (126,131). For the knee, the prevalence of OA was 15.5% for the elite, 4.2% for the non-elite and 1.6% in the control group (126). For the hip, the prevalence of OA was 14% for the elite players and 4.2% in non-elite and control groups (131). However, in both of these studies age was the only confounder adjusted for, though the later still showed increased OA in the elite group after excluding players who had had a joint injury. Two British surveys reported the prevalence of lower limb OA in ex-professional soccer players to be 49% (132) and 32% (127), with the knee being the most common site. Compared to controls, Spector *et al* (133) found former elite female athletes were 2.5 to 3.7 times more likely to have osteophytes in the knee and hip. Interestingly, the authors concluded that the length of sports practice was likely to be the important

factor and not the 'elitness' per se. In a review of studies on runners, Lane *et al* (134) concluded that the risk of knee OA may be increased by running at a competitive level but not at a recreational level. This body of literature has mainly focused on elite sporting populations who have been subjected to large amounts of training, the findings of which are unlikely to be pertinent to the general population.

Physical education teachers have been studied to assess the effects of moderate exercise. Eastmond and colleagues (135) found no difference in ROA of the hips and knees between female physical education teachers aged 46-60 years and historical, population based controls. However, historical groups may not be a valid comparision group. Nevertheless, similar finding were reported by White *et al* (136) in which female physical education teachers did not have increased rates of hip or knee ROA, and were actually seen to have lower rates of knee OA compared with age matched controls. In contrast, a study of 571 graduates from a Swedish training facility had higher rates of self reported knee OA than the comparison group (137). However, radiographs were not taken in this study and therefore the prevalence of radiographic OA cannot be ascertained. Similarly, previous knee injury was not taken into account in these studies despite higher reported rates in the teachers (137). It is also difficult to compare the extent of sports participation in these reports. On a side note, Manninen *et al* (56) show that moderate recreational exercise was associated with a decrease in the risk of knee OA requiring arthroplasty. All of the aforementioned epidemiological studies, including those on elite sporting populations have been retrospective in design and subject to many biases. As such, they do not provide strong evidence of cause and effect, that is, they do not allow us to conclude that exercise leads the development of OA. For this, we need to examine prospective studies.

In one prospective study, Lane *et al* (138,139) showed in 35 running subjects and 38 age matched controls (mean age 63 years), recreational running did not accelerate the development of radiographic or clinical OA of the knees. An eight year follow-up of the Framingham cohort (mean age 70.5 years) showed that for each increase in level of physical activity, there was a higher risk of knee OA (140). In fact, patients in the highest quartile of physical activity at baseline had 3.3 times the odds of developing OA compared with those in the lowest quartile. This was independent of other risk factors, including knee injury, and was similar for people with and without symptoms of knee OA. Subjects in this cohort were extremely sedentary, and as such the highest quartile of physical activity would probably correspond to normal ranges in a younger population. They also showed that the number of hours per day of heavy physical activity was associated with an increased risk of incident knee ROA, particularly for those with a high BMI (141). On a positive note, two further studies of the Framingham cohort revealed that there was no increased risk of knee OA for those participating in habitual physical activity (55) or light and moderate activities (141) after adjusting for age, BMI, knee injury, smoking and education. Number of blocks walked and number of flights of stairs climbed was also not related to OA. In a UK based population (median age 75.8 years), Cooper *et al* (46) showed that after 5.1 years, the odds of incident but not progressive radiographic OA were increased by a history of regular sports participation. Interestingly, this analysis was not adjusted for previous knee injury, despite the authors also reporting it to be a predictor of incident OA in this population.

In all studies on physical activity and incident and progressive OA, physical activity has been assessed using questionnaires. The limitations of questionnaires to measure physical activity are well documented (142-144) and include recall bias,

floor effects, and a variety of output units. Although not being physical activity per se, one prospective study has reported on an objective measure, that is knee extensor strength. Slemenda *et al* (99) showed that increased quadriceps strength may be a protective mechanism guarding against the onset of OA in women. More specifically, baseline quadriceps strength relative to body weight or to lower extremity muscle mass was 15-18% lower in women who developed radiographic evidence of knee OA compared to women whose radiographs remained normal. This was not true for men, whose baseline quadriceps strength was not a predictor of incident knee ROA.

Recently, novel imaging modalities such as magnetic resonance imaging (MRI) have made important contributions to our understanding of OA. MRI visualises all components of the joint simultaneously and has been validated as a measure of articular cartilage volume in healthy individuals (145), those with OA (146) and children (147). Our group has reported both cross-sectional and longitudinal positive associations between physical activity and cartilage development in children (148). We have also shown that increased muscle mass is strongly associated with medial tibial cartilage volume and a reduction in the loss of medial and lateral tibial cartilage over 2 years in healthy middle-aged people (149). Furthermore, knee injury, that is ruptured anterior cruciate ligament, has been associated with MRI evidence of cartilage thinning, thickening of subchondral bone trabeculae and bone oedema around 4 to 6 years post injury (150,151).

Glycosaminoglycan (GAG) content, a possible indicator of cartilage quality, has also been estimated by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) with results expressed as the change in the T1 relaxation time in the presence of Gd-DTPA (T1[Gd]) (152). GAGs may represent cartilage quality as they are building blocks of proteoglycans and are crucial for the viscoelastic properties of

cartilage. Roos and Dahlberg (152) randomised 45 subjects (mean age 46 years) who had undergone partial medial meniscus resection 3-5 years earlier to supervised moderate exercise 3 times weekly for 4 months or to a control group. They reported a significant improvement in the T1(Gd) of the exercise group compared with the control group and a strong correlation between self-reported change in physical activity and change in the T1(Gd).

The controversy surrounding the issue of exercise and OA warrants urgent attention given four separate guidelines for the management of lower-limb OA (American College of Rheumatology, European League Against Rheumatism, Algorithms for the diagnosis and Management of Musculoskeletal Complains and Institute for Clinical Systems Improvement) include exercise as one of their recommendations. Similarly muscle-strengthening interventions are now a major component of the usual treatment program for patients with knee OA, despite the little information on their effect on disease prevention and/or progression. This is particularly relevant given that both bone size and rate of cartilage loss have been identified as independent predictors of knee replacement in a longitudinal study (153). Lastly, there have been no studies in adults that have investigated the role of physical fitness on knee structural changes.

Aim

The aim of this longitudinal study was to describe the associations between strength, endurance fitness and self-reported physical activity, and structural change of the knee joint in a convenience sample of adult male and female subjects.

5.2 Materials and Methods

Subjects

The study was carried out in Southern Tasmania primarily in the capital city of Hobart from June 2000 until December 2001, with the follow-up data collected approximately two years later. A convenience sample was utilised for this study, in that the study was designed to examine genetic mechanisms of OA. Subjects (mean age: 45 years at baseline [range 26-61]) were selected from two sources. Half the subjects were the adult children of subjects who had had a knee replacement performed for primary knee osteoarthritis at any Hobart hospital in the years 1996-2000 (response rate 71%). This diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiograph where possible. The other half was randomly selected age- and sex-matched controls (response rate: 40%). The controls were selected by computer generated random numbers from the most recent version of the electoral role (2000). Subjects from either group were excluded on the basis of contraindication to MR imaging (including metal sutures, presence of shrapnel, iron filing in eye and claustrophobia). No women were on hormone replacement therapy at the time of the study.

Anthropometrics

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as kg/m^2. Knee pain was determined by self-administered questionnaire if subjects answered yes to the following question: have you had knee pain for more than 24 hours in the past 12

months or daily pain on more than 30 days in the last year? There was no discrimination between types of knee pain.

Physical activity measures

Physical activity measures included physical work capacity, lower limb muscle strength and questionnaire items. Lower limb muscle strength was measured to the nearest 1.0 kg using a dynamometer (TTM Muscle Meter, Tokyo, Japan). In our opinion, the muscles measured with this technique were primarily the quadriceps and hip extensors as evidence by the high correlation of 0.78 between this test and a specific test of quadriceps function (S Foley *et al*, unpublished). Subjects were asked to stand on the dynamometer with a straight back, flat against the wall, holding a hand bar with an overhand grip. Subjects' knees were flexed until an angle of 115° was obtained at which the bar was attached to the dynamometer via a chain. Subjects kept a firm grip on the bar and attempted to extend at the hip and knee. Subjects were instructed in each technique prior to testing and each measure was performed twice. Repeatability estimates [intraclass correlation coefficient (ICC)] for lower limb muscle strength were 0.91.

Physical work capacity was assessed by use of a bicycle ergometer (154). Subjects were asked to cycle at a constant 60 rpm for 3 min each at three successively increasing but submaximal workloads. Heart rate was recorded at one-minute intervals at each workload using an electronic heart rate monitor. Work capacity at 170 beats/min (PWC_{170}) was assessed by linear regression with extrapolation of the line of best fit to a heart rate of 170 beats/min. The PWC_{170} was not considered a technically adequately measure unless subjects had spent a minimum of two minutes at each workload and the pulse rate increased by at least 5 beats/min with increasing

workloads. Repeatability was not assessed in our subjects but has previously been reported as 0.92 (155).

Physical activity was measured retrospectively using a questionnaire (156) that was modified after piloting to include popular Australian sports. The test-retest Spearman correlation of overall leisure physical activity in hours/week over the last year was found to be 0.66. This questionnaire has demonstrated predictive validity in our hands for children and adolescents (147). The questionnaire has items on days of either strenuous activity or light activity for greater than 20 minutes in the last two weeks [(1) none, (2) 1-2 days, (3) 3-5 days, (4) 4-5 days, (4) 6-8 days, (5) 9 or more days]; daily television watching in the last week [(1) none, (2) 1 or less hours, (3) 2-3 h, (4) 4-5 h (4) 6 or more]; number of competitive sports in the past 12 months [(1) none, (2) one, (3) two, (4) three (5) four for more] and activities done at least 10 times in the last month.

X-ray

A standing anteroposterior (AP) semi-flexed view of the right knee was performed in all subjects. Radiographs were then assessed utilising the Altman atlas (108). Each of the following was assessed on a scale of 0-3: medial joint space narrowing (JSN), lateral JSN, medial femoral osteophytes, medial tibial osteophytes, lateral femoral osteophytes and lateral tibial osteophytes. Each score was arrived at by consensus with two readers (GJ, FS) simultaneously assessing the radiograph with immediate reference to the atlas. Reproducibility was assessed using the same process in 50 radiographs, 2 weeks apart and yielded an ICC of 0.99 for osteophytes and 0.98 for joint space narrowing. This may represent an overestimate of the actual agreement owing to the high proportion of normal radiographs. However, this method also has

very high reproducibility in our group for radiographic osteoarthritis (ROA) of the hands with ICCs of 0.94-0.98 (111).

Cartilage volume assessment

MRI scans of the right knee were performed on two occasions at baseline and follow-up. Knee cartilage volume was determined by means of image processing on an independent workstation using the software program Osiris (University Hospital of Geneva, Switzerland) as previously described (147). Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH) with use of a commercial transmit-receive extremity coil. The following image sequence was used: a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 msecs; echo time 12 msec; field of view 16 cm; 60 partitions; 512 x 512 matrix; acquisition time 11 min 56 sec; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 x 0.31 (512 x 512 pixels). The volume of individual cartilage plates (medial tibial, lateral tibial and patella) was isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. Femoral cartilage volume was not assessed as we have previously established that the two tibial sites and the patella site correlate strongly with this site (157). Using this method we had high intra and inter-observer reproducibility. Inter observer reproducibility was assessed in 30 knees by the same reader twice, approximately one

month apart. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial and 2.2% for lateral tibial (147).

Cartilage defect assessment

Knee cartilage defects were determined by means of image processing on an independent workstation by one observer (CD) using Osiris. The cartilage defects were graded (158-160) on both occasions at medial tibial, medial femoral, lateral tibial, lateral femoral and patellar sites as follows: grade 0, normal cartilage; grade 1, focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full-thickness chondral wear with exposure of subchondral bone. A cartilage defect also had to be present in at least two consecutive slices. The cartilage was considered to be normal if the band of intermediate signal intensity had a uniform thickness. The cartilage defects were re-graded one month later and the average scores of cartilage defects at medial tibiofemoral (0-8) and lateral tibiofemoral (0-8) were used in analysis. The reader was unaware of the initial result at the time of the second reading. Intraobserver reliability (expressed as ICC) was 0.89-0.94 and interobserver reliability was 0.85-0.90 (158-160).

Tibial plateau area assessment

Tibial plateau bone area was determined by means of image processing on an independent work station by one observer using Osiris as previously described (157). To transform the images to the axial plane, the Analyses Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was

determined by creating a composite measure from the three input images closest to the knee joint line after reformatting in the axial plane (approximately 5 mm from the joint line). The areas of the medial and lateral tibial plateau were then directly measured from these images. Reliability was assessed in 30 knees by the same reader twice, approximately one month apart. The CVs for these measures in our group are 2.2-2.6% (161).

Statistics

One-way ANOVA tests were used for comparisons of means. The chi-square test was used to compare nominal characteristics between groups. Least significant criteria was applied to investigate within group differences where

$$lsd = t_{\alpha/2[\text{error df}]}\sqrt{\frac{2(MSE)}{m}}$$

Rate of change in cartilage volume were calculated both as the absolute change per annum, $(v_1 - v_0)/t$, and as the percentage change per annum, $100(v_1 - v_0)/v_0t$, where v_0 is cartilage volume at baseline, v_1 is cartilage volume at follow-up and t is the time between scan in years. Change in tibial bone area was calculated in the same manner. Changes in cartilage defects were calculated by subtracting cartilage defect scores at baseline from cartilage defect scores at follow-up. A change in cartilage defects >=1 was defined as an increase in cartilage defects and a change in cartilage defects <=-1 was defined as a decrease in cartilage defects. Multiple linear regression techniques were used to explore the possible physical activity measures affecting the rate of change in cartilage volume and tibial bone area, with unstandardized regression coefficients presented. For changes in cartilage defect scores in individual

compartments, the range and distribution were such that basic assumptions for applying linear regression did not hold. Logistic regression analysis was used to examine the associations between progression of knee cartilage defects and physical activity variables.

Although associations did not differ in offspring and controls, we adjusted all associations for offspring-control status due to the convenience nature of this sample. Furthermore, multivariate results were age and sex adjusted (as well as ROA and weight where appropriate) due to possible confounding by these factors. A model was also constructed containing the physical activity variable, sex and their interaction term (physical activity x sex).

Statistical significance was determined based on the *P*-value for the interaction term. A *p*-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 9.0 for windows (StataCorp LP).

5.3 Results

A total of 325 subjects completed the study (87% of those originally studied). The mean interval between measurements was 2.3 y (range 1.8–2.6). Demographic and study factors are presented in Table 5.1. This was a young sample with an average age of 45 years at baseline (range 26-61). When subjects were examined by categories of PWC_{170} and change in lower limb muscle strength, there was a significant difference in the proportion of males and females. In addition, the height and weight of subjects differed between groups, with those who had a significant decrease in lower limb muscle strength and PWC_{170} being taller and heavier. BMI (both lowest in the no change group) and the percentage of subjects who had

progression of lateral defects (both lowest in the no change group), was significantly different between categories of PWC_{170}, whereas change in medial tibial plateau area differed significantly between categories of lower limb muscle strength (lowest in the decrease group and highest in the no change group).

Table 5.1. Characteristics of participants by change in PWC_{170} and lower limb muscle strength over 2.3 y

	Decrease	No change	Increase	*P* value
ΔPhysical work capacity at 170 beats/min	n = 34	n = 248	n = 9	
Sex (Female) (%)	28	63	55	<0.001†
Age (years)	46.1 ± 6.1	45.4 ± 6.4	44.5 ± 8.6	0.46
Height (cm)	175.6 ± 8.2	168.1 ± 8.1	169.3 ± 8.9	<0.001
Weight (kg)	92.5 ± 18.4	74.7 ± 13.3	79.5 ± 16.4	<0.001
BMI (kg/m2)	30.0 ± 6.1	26.4 ± 4.2	27.7 ± 5.0	<0.001
Change in BMI	0.92 ± 2.1	0.62 ± 1.6	0.07 ± 1.8	0.10
Radiographic osteoarthritis (%)	26	16	14	0.21†
% Change in cartilage volume per yr				
Medial	-2.8 ± 4.5	-2.4 ± 4.1	-3.3 ± 3.7	0.40
Lateral	-2.1 ± 4.1	-1.3 ± 3.4	-2.4 ± 2.9	0.07
% Change in tibial plateau area per yr				
Medial	-0.01 ± 1.6	0.57 ± 1.8	0.10 ± 1.8	0.08
Lateral	-0.04 ± 3.0	-0.01 ± 2.7	-0.17 ± 2.8	0.95
Progression of cartilage defects (%)				
Medial	35	19	23	0.07†
Lateral	30	17	32	0.027†
ΔLower limb muscle strength (kg)	n = 83	n = 200	n = 20	
Sex (Female) (%)	40	66	54	<0.001†
Age (years)	46.2 ± 5.9	45.3 ± 6.5	44.4 ± 8.7	0.24
Height (cm)	171.4 ± 8.7	167.7 ± 8.2	170.4 ± 8.7	0.002
Weight (kg)	82.6 ± 17.6	75.3 ± 14.9	78.1 ± 13.8	0.002
BMI (kg/m2)	28.1 ± 5.4	26.7 ± 4.7	26.9 ± 4.1	0.10
Change in BMI	0.56 ± 1.5	0.61 ± 1.7	0.61 ± 2.2	0.97
Radiographic osteoarthritis (%)	15	18	17	0.80†
% Change in cartilage volume per yr				
Medial	-2.3 ± 4.9	-2.6 ± 3.9	-2.8 ± 3.6	0.79
Lateral	-1.4 ± 3.3	-1.4 ± 3.5	-2.2 ± 3.3	0.36
% Change in tibial plateau area per yr				
Medial	0.89 ± 1.6	0.34 ± 1.8	0.09 ± 1.9	0.025
Lateral	0.41 ± 2.4	-0.11 ± 2.8	-0.51 ± 3.0	0.18
Progression of cartilage defects (%)				
Medial	23	19	30	0.24†
Lateral	24	18	23	0.42†

*Except where otherwise indicated, values are mean ± SD. BMI = body mass index. Change in PWC_{170} and lower limb muscle strength determined by least significant criterion. †Chi-Square test, all others ANOVA tests.

Analysis of the effect of baseline work capacity on the rate of annual change of cartilage volume (%) revealed a significant interaction between sex and PWC_{170} (p=0.09-0.004), therefore the results are presented separately for males and females (Table 5.2). In univariate analysis, for females, the higher the PWC_{170} at baseline, the greater the rate of loss in cartilage volume (%) in the medial, lateral and total compartments. After adjustment for confounders, this relationship persisted for lateral and total compartments only. Conversely, in both sexes, lower limb muscle strength was positively associated with annual cartilage change in the total compartment, with no other significant associations noted.

For tibial plateau bone area, there was again a significant interaction between sex and PWC_{170} (Table 5.2). In univariate analysis there was a significant negative association between PWC_{170} and annual % change in lateral and total tibial plateau area for males (p=0.03 and p=0.04 respectively), which did not persist after adjusting for confounders. Likewise, number of competitive sports was negatively associated with annual change of lateral tibial plateau area (p=0.04) but did also not persist after adjustment for age, sex, case/control status, lateral joint space narrowing and initial bone area. In multivariate analysis, in both sexes, lower limb muscle strength was significantly positively associated with annual % change of lateral and total tibial plateau area, with borderline significance in the medial compartment. In addition, there was a positive relationship between PWC_{170} and annual change of the lateral and total tibial plateau area for females. There was also a significant beneficial association between annual changes in PWC_{170} and % change in medial, lateral and total cartilage volume per year (Figure 5.1 and Table 5.3). Sensitivity analyses demonstrated that no specific outlies significantly affects the relationship (data not shown)

Changes in PWC_{170} were not related to annual % change in tibial plateau area. On the contrary, annual changes in lower limb muscle strength were negatively

associated with annual % changes in lateral tibial and total tibial plateau area (Figure 5.2), however when baseline muscle strength was added to the model, the results were weakened (total-tibial p=0.01, medial p=0.07 and lateral p=0.07). Changes in muscle strength were not related to annual % change in cartilage volume.

For both univariate and multivariate logistic analyses (age, sex, BMI, case/control status, baseline defect score, baseline cartilage volume and bone area adjusted) of cartilage defects, sessions of strenuous exercise was significantly associated with a reduction in the odds of lateral knee cartilage defects progressing over 2.3 years [odds ratio (OR) = 0.73, p=0.039]. Although not significant, there was a consistent trend for medial cartilage defects decreasing with strenuous activity (OR=0.86, p=0.24). No other physical activity measures demonstrated a significant association with progression of knee cartilage defects (data not shown).

There were no significant differences in the associations between physical activity and knee structural changes when cases (offspring) and controls were examined separately (data not shown) thus both groups were combined for all analyses. These results were also independent of knee pain and/or past knee injury (data not shown).

Table 5.2. Relationship between annual percent change of cartilage volume and tibial plateau area, and baseline physical activity measures*

	Regression coefficient		
	Univariable analysis (95% CI)	Multivariable analysis† ‡ (95 % CI)	*P* value
Tibial cartilage volume, % µl/year †			
Medial			
PWC_{170} (per 10 Watts)			
Males	-0.01 (-0.09, 0.07)	0.03 (-0.04, 0.10)	0.39
Females	-0.11 (-0.20, -0.01)	-0.08 (-0.16, 0.01)	0.10
Lower limb muscle strength (kg)	0.01 (0.0004, 0.02)	0.01 (-0.01, 0.02)	0.22
Lateral			
PWC_{170} (per 10 Watts)			
Males	0.04 (-0.03, 0.10)	0.06 (-0.004, 0.12)	0.07
Females	-0.12 (-0.20, -0.03)	-0.09 (-0.18, -0.01)	0.03
Lower limb muscle strength (kg)	0.006 (-0.002, 0.014)	0.01 (-0.002, 0.02)	0.09
Total			
PWC_{170} (per 10 Watts)			
Males	0.01 (-0.04, 0.07)	0.04 (-0.02, 0.09)	0.17
Females	-0.09 (-0.16, -0.02)	-0.07 (-0.14, -0.007)	0.03
Lower limb muscle strength (kg)	0.005 (-0.002, 0.012)	0.01 (0.001, 0.02)	0.04
Tibial plateau area, % mm^2/year ‡			
Medial			
PWC_{170} (per 10 Watts)			
Males	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)	0.70
Females	-0.0004 (-0.05, 0.05)	0.02 (-0.03, 0.06)	0.47
Lower limb muscle strength (kg)	0.005 (0.001, 0.009)	0.007 (-0.0004, 0.014)	0.06
Lateral			
PWC_{170} (per 10 Watts)			
Males	-0.06 (-0.11, -0.006)	-0.04 (-0.09, 0.02)	0.18
Females	0.07 (-0.003, 0.13)	0.08 (0.01, 0.14)	0.02
Lower limb muscle strength (kg)	0.006 (-0.001, 0.012)	0.01 (0.004, 0.02)	0.009
Total tibial			
PWC_{170} (per 10 Watts)			
Males	-0.03 (-0.06, -0.001)	-0.02 (-0.05, 0.008)	0.15
Females	0.03 (-0.01, 0.06)	0.04 (0.002, 0.08)	0.04
Lower limb muscle strength (kg)	0.005 (0.002, 0.009)	0.009 (0.003, 0.014)	0.005

95% CI: 95% confidence interval; PWC_{170}: physical work capacity at 170-beats/min (adjusted for weight). †Adjusted for sex, age, case/control status, initial cartilage volume and bone area. ‡ Adjusted for sex, age, case/control status, initial bone area and joint space narrowing.

Table 5.3. Association between change in physical activity measures and annual percent change of cartilage volume and tibial plateau area*

	Regression coefficient		*P* value
	Univariable analysis (95% CI)	Multivariable analysis† (95 % CI)	
Tibial cartilage volume, % µl/year			
Medial			
PWC_{170} (per 10 Watts/yr)	0.15 (0.02, 0.27)	0.16 (0.03, 0.29)	0.02
Lower limb muscle strength (kg/yr)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	0.39
Lateral			
PWC_{170} (per 10 Watts/yr)	0.14 (0.04, 0.25)	0.14 (0.03, 0.25)	0.01
Lower limb muscle strength (kg/yr)	-0.02 (-0.05, 0.01)	-0.02 (-0.05, 0.01)	0.19
Total			
PWC_{170} (per 10 Watts/yr)	0.12 (0.03, 0.22)	0.11 (0.01, 0.20)	0.03
Lower limb muscle strength (kg/yr)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	0.39
Tibial plateau area, % mm^2/year			
Medial			
PWC_{170} (per 10 Watts/yr)	0.04 (-0.02, 0.09)	0.04 (-0.01, 0.10)	0.12
Lower limb muscle strength (kg/yr)	-0.01 (-0.03, 0.004)	-0.02 (-0.03, 0.001)	0.06
Lateral			
PWC_{170} (per 10 Watts/yr)	-0.004 (-0.09, 0.08)	0.01 (-0.08, 0.10)	0.82
Lower limb muscle strength (kg/yr)	-0.03 (-0.06, -0.01)	-0.03 (-0.06, -0.002)	0.03
Total tibial			
PWC_{170} (per 10 Watts/yr)	0.02 (-0.03, 0.07)	0.03 (-0.02, 0.08)	0.21
Lower limb muscle strength (kg/yr)	-0.02 (-0.03, -0.01)	-0.02 (-0.04, -0.01)	0.004

% CI: 95% confidence interval; PWC_{170}: physical work capacity at 170-beats/min †Adjusted for age, sex, change in BMI and case/control status

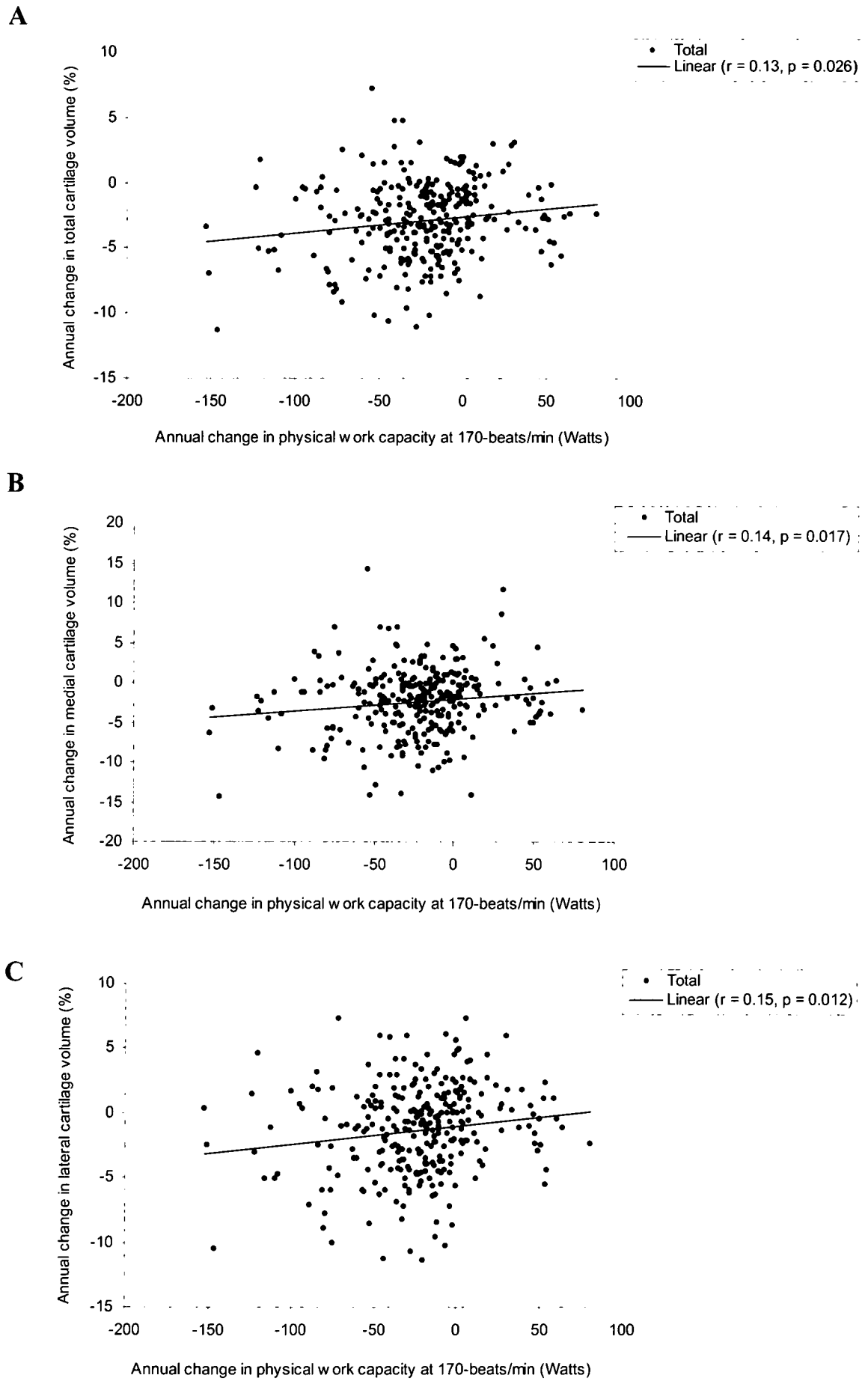
A
Total
Linear (r = 0.13, p = 0.026)
Annual change in total cartilage volume (%)
10
5
0
-5
-10
-15
-200
-150
-100
-50
0
50
100
Annual change in physical work capacity at 170-beats/min (Watts)
B
Total
Linear (r = 0.14, p = 0.017)
Annual change in medial cartilage volume (%)
20
15
10
5
0
-5
-10
-15
-20
-200
-150
-100
-50
0
50
100
Annual change in physical work capacity at 170-beats/min (Watts)
C
Total
Linear (r = 0.15, p = 0.012)
Annual change in lateral cartilage volume (%)
10
5
0
-5
-10
-15
-200
-150
-100
-50
0
50
100
Annual change in physical work capacity at 170-beats/min (Watts)

Figure 5.1

Figure 5.1. Association between annual change in cartilage volume (%) and change in PWC at 170-beats/min over 2.3 years. r was adjusted for age, sex, change in BMI and case/control status. There was a modest but significant positive association between annual percent cartilage volume change and change in physical work capacity at 170-beats/min in the total sample in the medial, lateral and total compartment. A = Total, B = Medial and C = Lateral

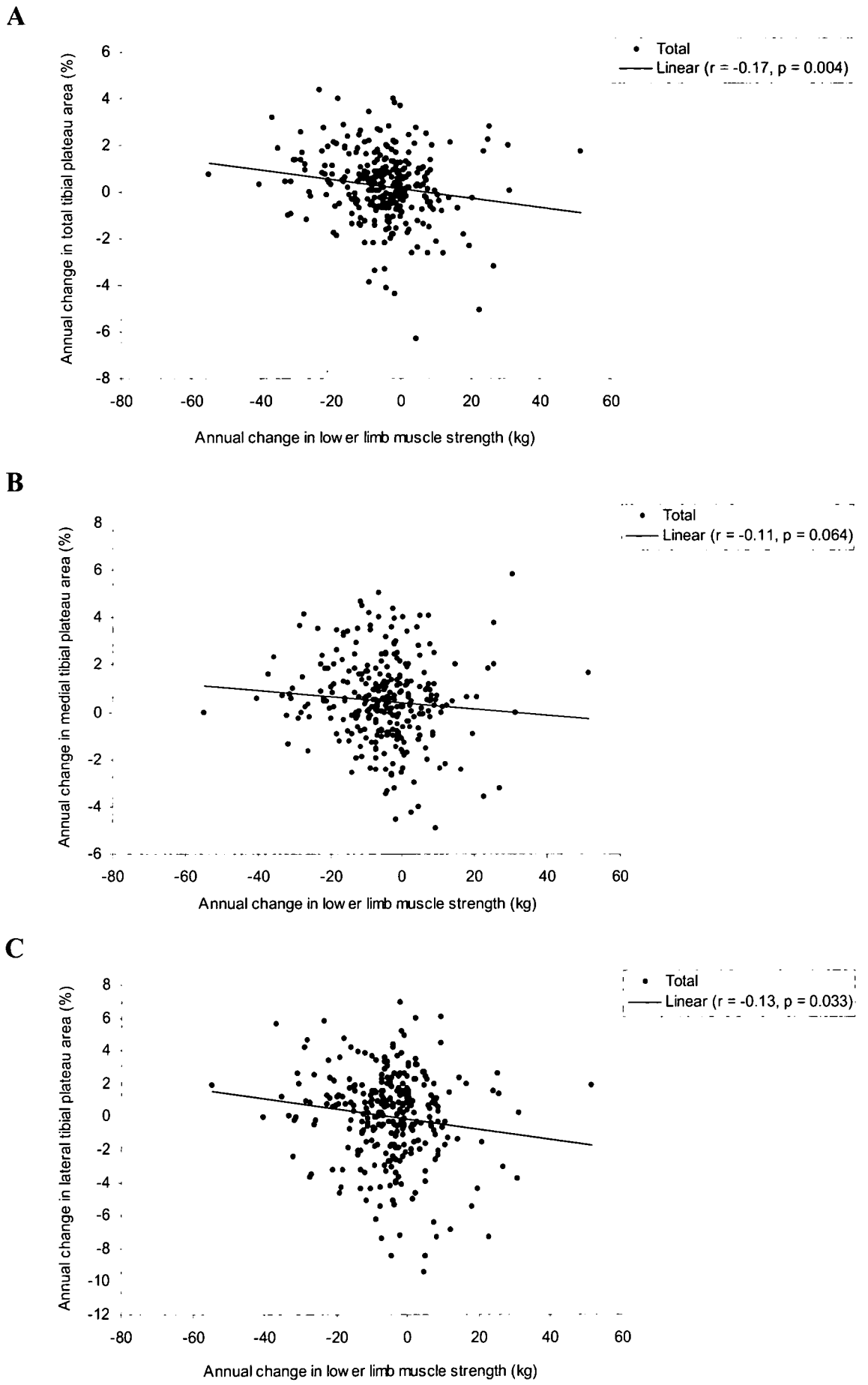
A
Annual change in total tibial plateau area (%)
6
4
2
0
-2
-4
-6
-8
-80
-60
-40
-20
0
20
40
60
Annual change in lower limb muscle strength (kg)
Total
Linear (r = -0.17, p = 0.004)
B
Annual change in medial tibial plateau area (%)
8
6
4
2
0
-2
-4
-6
-80
-60
-40
-20
0
20
40
60
Annual change in lower limb muscle strength (kg)
Total
Linear (r = -0.11, p = 0.064)
C
Annual change in lateral tibial plateau area (%)
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-80
-60
-40
-20
0
20
40
60
Annual change in lower limb muscle strength (kg)
Total
Linear (r = -0.13, p = 0.033)

Figure 5.2

Figure 5.2. Association between annual change in bone area (%) and change in lower limb muscle strength (kg) over 2.3 years. r was adjusted for age, sex, change in BMI and case/control status. There was a negative association between annual percent bone area change and change in lower limb muscle strength in the lateral and total-tibial compartment in the total sample. A = Total, B = Medial and C = Lateral.

5.4 Discussion

To our knowledge, this is the first study to describe the associations between fitness and physical activity, and knee structural change. In this longitudinal study we demonstrated that lower limb muscle strength was positively associated with both total cartilage volume and tibial plateau area change per year. In females, there was a deleterious relationship between PWC_{170} and annual change in lateral and total cartilage volume and tibial bone area. Furthermore, annual change in lower limb muscle strength was negatively associated with change in lateral and total tibial plateau area annually, where as changes in PWC_{170} were positively associated with annual changes in medial, lateral and total cartilage volume. Strenuous exercise was associated with a reduction in the odds of defects progressing. These associations were modest in magnitude, typically explaining less than 4% of the variance in the data, but indicate that the relationship between physical activity and change in knee structure is complex and may have differential effects on both bone and cartilage.

The clinical significance of structural change in the knee is gradually emerging. Every 25 mm increase in tibial bone size at baseline increases the odds of knee replacement by 5% per annum (153). In our study population, subjects in the lowest quartile of change in muscle strength, that is, subjects who lost the most muscle strength, had an average gain of bone area of 26 mm/yr whereas people in the highest quartile had a loss of -1.6 mm/yr. This difference would lead to a 5.6% per annum increase in the odds of knee replacement. Similarly, cartilage volume loss is also a predictor of joint replacement (162) with a 1% increase in the rate of cartilage loss increasing the risk of undergoing knee replacement by 5% per annum (153). Again, subjects in the lowest quartile of baseline muscle strength would have a 3.8% per year increased odds of undergoing knee replacement compared to subjects in the

highest muscle strength quartile. Furthermore, given an end stage knee has lost 60% of it cartilage volume (153,163); a person in the lowest quartile of muscle strength will reach end stage loss 5 years earlier than those in the highest quartile (given the overall rate of loss in controls in this sample). Although these changes are modest in magnitude, these effects would be important at a population level.

Strength is largely a reflection of muscle size (164). As such, the significant association between strength and annual change in total cartilage volume is in accordance with the results of Cicuttini *et al.* who recently showed that muscle mass was associated with a reduction in the rate of loss of tibial cartilage in a healthy population (149). The quadriceps attenuates load across the knee joint and is important in providing anterior-posterior stability (165). The muscle dysfunction hypothesis suggests that when the muscles cannot contract properly (i.e. age, disuse atrophy or injury induced weakness), more force is transmitted to the bone, which leads to microtrabecular damage and eventually sclerosis that could alter the stresses across the articular cartilage (166). The unfavourable relationship between lower limb muscle strength at baseline and increases in bone area may be consistent with this as larger bone may alter cartilage loading and, thus, represents a maladaptive response to load. However, the inverse association between change in muscle strength and change in bone area was beneficial. The reasons behind this discrepancy are unclear. Both baseline muscle strength and change in muscle strength are under both genetic and environmental control and there may be differential genetic effects such that change in muscle strength may more accurately reflect environmental change. The negative association between baseline muscle strength and change in muscle strength (due to ceiling/floor effects) may also explain the opposite effects on joint structure. Overall,

the data suggests that programs aimed at increasing muscle strength may still have good effects on tibial bone area.

The PWC_{170} test is essentially a test of fitness. This also has both genetic and environmental components. The baseline association most likely reflects both (with a genetic preponderance) whereas the association between change in PWC_{170} and annual percent change in cartilage volume is likely to be mainly environmental, reflecting changes in fitness due to changes in activity as there was no significant genetic component to change in PWC_{170} in our sample (G Zhai *et al*, unpublished). This could explain the apparent contradictions between the two analyses with women with higher PWC_{170} having higher rates of loss but those who increased PWC_{170} had higher rates of increase in cartilage volume. The latter relationship is consistent with mouse studies, in which wheel running lead to strengthening of the ligaments and muscles around the knee joint, building up improved dynamic stability and shock absorbing capacity needed during loading movements. Furthermore, Lapvetelainen *et al.* hypothesised that the locomotion may have also had an effect on the structure and strength of the collagen network of articular cartilage (122). In a randomised trial, human cartilage responded to moderate exercise by increasing its GAG content, which may improve the biomechanical properties of the cartilage (152). On the contrary, increased cartilage volume may be a result of aggrecan loss from the matrix and increased water content, which is an early event in the onset of OA in some subjects (167).

In females, there was a positive association between PWC_{170} at baseline (but not change) and annual percent change in tibial plateau area. Peak knee adduction moment has been shown to positively correlate with medial tibial plateau bone area (168), thus supporting the notion that mechanical load plays a role in the regulation of

bone remodelling. Oettimeier showed in dogs that below the intact articular surface, the articular cartilage and subchondral bone may become thicker following mechanical loading. This process however, may not be available when sclerosis is further advanced and consequently impairs the biomechanical function of the surrounding tissues (57). Our results add to this and indicate a possible deleterious effect on the joint.

It is interesting to note that we observed no significant associations between PWC_{170} and strength, and chondral defects, despite increased bone area being a predictor of chondral defect progression (169). This observation still remains largely unexplained, although the finding that baseline strenuous exercise had a protective effect, independent of injury, is reassuring. The lack of consistent association with other questionnaire items most likely reflects the well known deficiencies of questionnaires compared to objective measures. It is possible that more accurate measures of actual activity such as pedometers may give different results.

The physical activity associations are complex but the observation that changes in PWC_{170} and lower limb muscle strength are both associated with knee structural changes are important for a number of reasons. Firstly, this indicates that articular cartilage and subchondral bone are dynamic structures that can respond to environmental manipulation, despite being under strong genetic control (170). Further to this, there is promise that exercise programs could be designed and implemented in those predisposed to OA; to delay or even prevent structural changes. Our results suggest that muscle strengthening is more likely to be beneficial than fitness training.

The current study has a number of potential limitations. Firstly, assessment of physical activity is problematic in epidemiological studies. While the questionnaire we used has good test-retest reliability, there is still a considerable margin for

measurement error. The likely effect of this is to decrease the strength of associations between physical activity and structural change, and lead to lower power to find moderate associations. Similarly, the questionnaire assesses leisure time physical activity and does not take into account occupation related physical activity. As such, the few associations noted in regard to questionnaire items, may be a result of exercise that does not constitute leisure time physical activity. The questionnaire also has limitations when focusing on specific sports thus it would be worthwhile to study inception cohorts of those participating in sports with different weight bearing properties to examine if there is variation in effect with different sports. Secondly, the current study was primarily designed to look at genetic mechanisms of knee OA and utilised a matched design. The matching was broken for the current study but adjustment for case-control status did not alter the results. Indeed, while there was a reduction in power, the results differed very little when offspring and controls were examined separately. Thirdly, while the sample is a convenience sample, Miettinen (171) states for an analytical cohort study to be generalizable to other populations, it does not have to be representative of the community from which it was selected provided it meets the following three key criteria regarding definition of eligible participants; adequate sample size; and a proper distribution of determinants, modifiers and confounders, all of which were met by this study. Lastly, measurement error associated with MRI may have weakened the associations. However, our assessment technique has high reproducibility in our group suggesting this is not of major concern.

In conclusion, this study suggests that knee cartilage volume and tibial plateau area are dynamic structures that can respond to physical stimuli. Greater muscle strength and endurance fitness, especially in women, may be protective against

cartilage loss, however it may also result in a maladaptive enlargement of subchondral bone in both sexes, suggesting physical activity may have both good and bad effects on the knee.

CHAPTER 6: MEASURES OF CHILDHOOD FITNESS AND BODY MASS INDEX ARE ASSOCIATED WITH BONE MASS IN ADULTHOOD: A 20 YEAR PROSPECTIVE STUDY

6.1 Introduction

Osteoporotic fractures are a major, and increasing, public health problem (172). Peak bone mass contributes more than 50% of the variation in bone mass until at least age 65 (173) and is therefore likely to be a major determinant of fracture risk later in life (174). The timing of peak bone mass is controversial with estimates ranging from age 16 to age 30 (174) though the majority of adult bone mass is laid down before age 17 years (69,70,175,176). Despite a lack of direct evidence, it is widely believed that interventions aimed at increasing peak bone mass may prevent osteoporosis and related fractures. Regular, weight-bearing exercise has received considerable attention of late as one strategy to increase peak bone mass.

Prospective studies have indicated that children who are active have greater increases in bone mass compared to those who are less active. In 470 boys and girls aged 8.2-16.5 years at baseline, Gunnes and Lehman (177) showed weight bearing physical activity predicted change in cortical and trabecular BMD, and had the greatest effect on trabecular BMD in children below 11 years of age. Slemenda *et al* (178) reported a 4-7% greater increase in aBMD for prepubertal children in the uppermost quartile of physical activity compared with those on the lowest quartile, while Vincente-Rodriguez *et al* (179) showed that femoral bone mass increased twice as much in a group of active boys compared to controls over a three year period. Bailey *et al* (180) analysed 6 years of data from 53 girls and 60 boys in which physical activity was measured biannually and bone mass annually. A 9% and 17% greater total body BMC was noted for active boys and girls over their inactive peers 1 year after the age of peak bone mineral content velocity. Although such studies contribute to the literature, they do not provide robust and causal inferences between

exercise and bone mass. For this we need to examine randomised controlled trials which provide more valid and reliable evidence.

Hind and Burrows (181) reviewed 22 randomised and non-randomised controlled trials on the effects of exercise and bone mineral accrual in children and adolescents. Of the 22 trials reviewed, 9 were conducted in prepubertal children, 8 in early pubertal and 5 in pubertal. Exercise interventions included games, dancing, resistance training and jumping exercises with durations being anywhere from 3 to 48 months long. Six trials (182-187) in pre pubertal children reported positive effects of exercise on bone with increases over 6-months ranging from 1.1% to 5.5%. Fuchs *et al's* (184) study, which demonstrated a 4.5 and 3.1% increase in boys and girls (mean age 7.6 years) femoral neck and spine BMC following a jumping intervention, was judged to have lowest risk for bias based on trial duration, compliance, sample size and adjustment for confounders. MacKelvie *et al* (185,188) also prescribed jumping exercises though the ground reaction forces were lower than that in Fuchs *et al*'s study. Their results were conflicting in that femoral neck BMC and bending strength increased in exercising boys (mean age 10.2 years) compare to controls (mean age 10.1 years) (185), whereas girls (mean age 10.1 years) did not show the same skeletal benefit (188). The only difference between studies were the length of intervention, with boys training for 20 months while girls only trained for only 7 months. Length of intervention cannot be the full explanation as in Fushs *et al*'s study and one by Bradney *et al* (183), interventions were 7 and 8 months respectively, and both reported substantial skeletal benefits.

All the studies in early pubertal children (188-193) showed a positive effect on bone accrual with effects ranging from 0.6% to 6.2%. The study in early pubertal children judged to have the lowest risk for bias was that by Iuliano-Burns *et al* (190).

They showed in four groups of 16 girls each (mean age 8.8 years), a 3% main effect of exercise at the tibia-fibula and also a calcium-exercise interaction at the femur. Similar in quality, MacKelvie *et al* (188) showed 7 months of jumping and circuit training in girls (mean age 9.9 years) could increase femoral neck estimated volumetric BMD, in addition to spine and femoral neck bone mass. Morris *et al* (194) demonstrated the greatest improvement in bone mass (femoral neck aBMD +10.3% [6-mnth +6.2%]) though selection bias was likely as selection to groups was decided by teachers and study drop-outs resulted in maturity status being more advanced in the exercise group. All studies but one (195) in early pubertal children included girls only. McKay *et al* (195) introduced "Bounce at the Bell", a novel exercise regime in which boy and girls (mean age 10.1 years) performed countermovement jumps for 3 minutes at each school bell. After 8 months, exercisers had significantly higher proximal femur and trochanter BMC, however the exercise group had also participated in more physical activity at baseline which may have confounded the results. Macdonald *et al* (196) reported on the implementation of Bounce at the Bell on a larger scale, in which tibial bone strength was enhanced in early pubertal males but not in females. Although the quality of these studies were variable and there were insufficient numbers to draw definitive conclusions, they do suggest early puberty may be an opportune time for bone adaptation to loading.

Of the 5 intervention studies in pubertal children, only 2 (197,198) showed a positive effect of exercise on bone mass (0.3% to 1.9%). The first, a 15.5 month double blind exercise and calcium intervention in girls (mean age 17.3 years), showed exercise + calcium augmented greater changes in bone measures compared to no exercise + placebo (197). The second study, also over 15 months, found increased Ward's triangle and femoral neck aBMD by 3.2% and 2.3% respectively. This study

had a large drop-out rate with only 16 girls (mean age 15.9) reaching follow-up. Two studies not to show an effect used resistance training (189,199) while the third employed jumping exercises (200). Whilst it appears the response of bone to exercise may be lessened in the later stages of puberty, this could partly be due to the poor quality of studies in pubertal children (i.e. limited by small sample sizes, varying exercise participation levels at baseline and lack of change in performance variables with training) and also the lack there of, particularly in boys.

Despite evidence that children's bones can adapt to weight-bearing exercise, uncertainty remains as to whether the effects are maintained in the long term. Retrospective (201-204) and cross-sectional studies (205-209) have provided limited insight into the effects of childhood exercise in the decades following attainment of peak bone mass. Unilateral loading studies suggest that high-impact loading, particularly before skeletal maturation is reached, positively influences adult bone mineral density (BMD) (203,208). Specifically, the side-to-side difference in arm bone mass of squash and tennis players was 2 to 4 times higher in the players who had started their careers before or at menarche compared to those who started more than 15 years after menarche (203).

Studies of retired athletes (201,202,206,207) suggest that adolescent bone gain may, at least partly persist despite reduced adult physical activity. Bass *et al* (201) reported the aBMD in retired gymnasts was 0.5-1.5 SD higher than the predicted mean in controls at all sites. There was no diminution across the 20 years since retirement despite the lower frequency and intensity of exercise. It has also be shown that self-reported hours of ballet class undertaken between 10 and 12 years is positively associated with the difference in BMD between dancers and controls at both the femoral neck and total hip (beta = 0.73 and 0.55 respectively) (202).

Karlsson *et al* (210) investigated whether the beneficial effect of weight lifting on aBMD was maintained in the long term in former weight lifters. The authors reported that aBMD values were significantly higher in former athletes aged 50-64 compared with control subjects, but no such favorable findings were observed in the study population above 65 years of age. Similarly, former male soccer players had no aBMD advantage compared with controls after 70 years of age (209) and their aBMD decreased linearly until approximately 25 years following retirement after which it plateaued (205,207). On the other hand, Duppe *et al* (206) reported that retired female soccer players aged 34-84 years had higher total body and hip bone mass compared to controls. In the context of reduction in the risk of fractures, Karlsson *et al* (205) showed the proportion of former soccer players with fragility fractures was slightly less than controls (2.1% vs 3.7%) but this was not significant and therefore concluded fracture rate was no lower than predicted in old age. These studies are prone to a number of biases and most focus on elite sporting populations which may not be pertinent to the general population. For example, selection bias may influence the results in that strong bones are likely to be highly influential in the ability to maintain participation for any length of time without injury. Furthermore, given the early pubertal years may be the opportune time and that professional sporting careers are not likely to begin until late adolescence or early adulthood, the studies in weight lifters and soccer players may have not captured the crucial period and therefore, cannot answer the question of whether the benefits of childhood activity persists into older age. Despite the potential flaws in these studies, recommendations for osteoporosis prevention to begin in childhood by means of weight-bearing exercise, have resulted (181,211).

One study has examined the relationship between physical activity in adolescence and early adult bone mass. 182 subjects, as part of the Amsterdam Growth and Health Longitudinal Study, had neuromotor and cardiopulmonary fitness measures during adolescence and young adulthood, followed by a DXA scan at age 28 (212). Neuro-motor fitness at age 13-16 years was shown to be positively related to spine and femoral neck aBMD at age 28 and that there was a trend for an association between adolescent cardiopulmonary fitness and spine aBMD at age 28. Although these results are encouraging, Kemper *et al* did not adjust for fitness at follow-up, thus we do not know if adolescent fitness was related to adult bone mass independent of the subjects current fitness level. This is important as cessation of exercise may be the Achilles heel of exercise induced bone mass gains and is particularly relevant in Kemper *et al*'s study as they also showed current (adult) fitness was associated with bone mass. Furthermore, given the starting age at baseline, the majority of subjects would have been in the later stages of maturity.

Body composition has also been implicated in the accrual of bone mass in children. Researchers have generally found bone mass in children and adolescents to be associated with both lean mass and fat mass, though the association tends to be stronger for lean mass (213-215). Young *et al* (216) measured female twins aged 8 to 25 years at baseline, and then again 2 to 6 times with an average time of 1.8 years between measurements. During linear growth, annual changes in total body BMC were associated with annual changes of 1.9% and 1.3% per kg in lean mass and fat mass respectively. They found however, that the most parsimonious models for spine and femoral neck aBMD accretion were those where lean mass alone was fitted. Rauch *et al* (217) reported that peak BMC accrual occurred within a year after maximal increases in total lean mass in boys and girls. Studies in prepubertal boys

have shown that changes in lean mass was the best predictor of changes in hip BMC and aBMD, with no relation found between changes in fat mass and bone accrual (179,218).

The influence of childhood body composition on adult bone mass is unclear. While studies on childhood exercise and adult bone mass can employ a retrospective design whereby activity during childhood is recalled; the same cannot really be used for childhood body composition. There have been no long-term follow-up studies in inception population cohorts that we are aware of. This would appear to be the most ideal way of assessing long term effects of skeletal loading and body composition in childhood as randomised trials would need to study thousands of children, continue the intervention and then follow them over many years, which is unlikely to ever be achieved.

Quantitative ultrasound (QUS) methods have been developed and introduced in recent years for the assessment of skeletal status. QUS parameters permit analysis of some physical properties of bone tissue, which in turn, are important determinants of bone stiffness, load failure, and fracture risk by providing additional information to bone mass alone (219). Measurements of bone QUS (quantitative ultrasound index [QUI], broadband ultrasound attenuation [BUA] and speed of sound [SOS]) predict fracture risk, with the strength of association for non spinal fractures being equivalent and additive to that of DXA derived BMD (220,221). A meta-analysis of heel QUS and fracture (220) showed that QUI was most strongly related to fracture risk followed equally by BUA and SOS. This meta-analysis was limited to females however, and included a range of QUS devices. Specifically looking at the fracture study that used the Sahara device (222), a 1 SD reduction in the three QUS variables

resulted in relative risks for hip fracture ranging from 2.2 (95% CIs: 1.7-3.0) to 2.4 (95% CIs: 1.8-3.2). In three studies that also included males (221,223,224) BUA was most strongly related to fracture risk followed by SOS. Thus, all three measures appear similar in terms of fracture risk in older age. Heel QUS has also been shown to discriminate adolescents who have fractured from those who have not (225) and two studies have found lower QUS measures at the phalanges in children with recent fracture compared to children without (226,227). Thus, it would not be unreasonable to infer that QUS is a valid measure of fracture risk throughout the entire lifespan. Lastly, since the heel is directly exposed to mechanical load (i.e. exercise, BMI) the calcaneum is an attractive site for quantifying the effects of loading.

Aim

The aim of this longitudinal study was to describe the associations between childhood physical performance measures, BMI and adult bone mass, as measured by QUS, in a cohort of children who were re-examined as young adults.

6.2 Materials and Methods

Subjects

In 1985 a representative Australia wide sample of 8,498 children (mean age 11 yrs) were measured as part of the Australian Schools Health and Fitness Survey (ASHFS). The study sample consisted of 9,000 school-children between the ages of 7 and 15 inclusive (500 in each age/sex stratum). The subjects were selected using two-stage probability sampling. The first stage involved the selection of schools. These were chosen with a probability proportional to the enrollment numbers of students aged 10 years in primary school and 14 in secondary school. Schools with more than

200 pupils were listed in ascending postal code order and then chosen using a random start, constant interval procedure. The school response rate was 90.1% (109/121). The second stage consisted of the random selection of 10 boys and 10 girls in each age group from each school. The sampling frame for this was the enrollment list provided by the school. 77.5% of parent and child consent was obtained in the initial sample. The ASHFS gathered extensive measures of health and fitness through various field and technical tests.

In 2001 and 2002, electoral rolls, telephone listings, the National Death Index, and contact with classmates were used to trace participants for the Childhood Determinants of Adult Health Study (CDAH). Traced individuals (n=6,840) were contacted in 2001-2005 and invited to participate in the follow-up study. 5,170 subjects enrolled in the study, with a total of 2,410 subjects attending a clinic at mean age 31 years (range 26-36 years). Calcaneal quantitative ultrasound (QUS) was performed on 1,434 of these subjects (17% of those originally studied). Reasons for not having a calcaneal QUS at follow-up included the machine being out of service (n=789), reduced protocol (n= 98) and other (i.e. machine not calibrated in time for early participants) (n=64).

Anthropometrics

Weight was measured to the nearest 0.5 kg in 1985 with beam or medical spring scales and 0.1 kg at follow-up with electronic scale (with shoes, socks and bulky clothing removed). In 1985, height was measured to the nearest 0.1cm using a KaWe height tape (KaWe Kirchner & Wilhelm, Asperg, Germany) or rigid measuring tape in, and a stadiometer (Invicta, Leicester, UK) was used at follow-up (with shoes and socks removed). Body mass index (BMI) was calculated as kg/m^2 for both time

points. To allow analysis of differing age groups, age and sex specific z scores were generated for childhood BMI. Z scores were derived from the whole ASHFS cohort, that is, a representative sample of Australian school children in 1985. Skinfold measurements were also obtained in 1985, allowing us to calculate an estimate of childhood lean mass (228).

Performance measures

Performance measures included a 1.6 km run, 50 m sprint, leg strength, standing long jump and bicycle ergometer test of physical work capacity at 170 beats/min (PWC_{170}). In 1985, leg strength and PWC_{170} were measured in only the 9, 12 and 15 year olds.

The 1.6 km run was assessed on a 400 m or 200 m grass track. Subjects were instructed on the number of laps to be completed and that the technique best employed for running the distance is to maintain a steady pace for the start and middle of the distance, and that they could increase speed at the end of the distance if they still felt comfortable and had the endurance. A score sheet was used to check off the number of laps completed by each subject. Timekeepers used stop watches and recorded subjects' times (minutes: seconds) as they passed the finish line.

The fifty meter sprint was run on a straight, level, 50m track at right angles to the wind direction. Subjects were given a thorough warm up with stretching and light jogging prior to testing. The subjects started behind the staring line in a standing position. There was only one trial, so the subjects were instructed to do their best and run as fast as possible until well past the finish line. Subjects ran in small groups with as many runners as there were timekeepers. The time was measured to the nearest $1/100^{th}$ of a second.

Leg strength was measured to the nearest 1.0 kg using a dynamometer (TTM Muscle Meter, Tokyo, Japan) identical to that described in Chapter 5. A repeatability estimate (intraclass correlation coefficient) was not assessed in this population but has previously been reported as 0.91 (147).

To assess standing long jump, the subject stood behind a line marked on the ground with feet slightly apart. A two foot take-off and landing was used, with swinging of the arms and bending of the knees to provide forward drive. Each subject was allowed two trials with the best score counted. The jump was repeated if the subject fell back or used a step at take-off. Distance was measured from the landing point at the closest part of the heel to the starting line (to the nearest centimetre).

Cardiorespiratory fitness was estimated based on physical work capacity at a heart rate of 170 beats per minute, which was assessed using a bicycle ergometer (154) identical to that described in Chapter 5. VO_{2max} is a universally accepted laboratory measure of cardiovascular fitness, but is unsuitable for field work, especially for a nation wide study such as the ASHFS. Furthermore, motivating children to achieve maximal effort is highly problematic. As a result, the most popular methodologies to predict VO_{2max} in children have utilized submaximal bicycle ergometry to determine the physical work capacity (PWC). PWC is safer, less expensive, more portable, and does not require the same level of motivation as a maximal test. In the ASHFS, 261 subjects also completed a VO_{2max} test. We found the correlation between PWC_{170} and VO_{2max} to be 0.83.

Leg strength, standing long jump and PWC_{170} were all measured at follow-up using exactly the same methods.

Quantitative ultrasound measurements

At follow-up, subjects had calcaneal QUS measurements using a single Sahara Clinical Bone Sonometer (Hologic Inc., MA, USA). The system consists of two sound transducers mounted coaxially on a motorized caliper. This enables direct contact with the heel through elastomer pads and an ultrasonic coupling gel. One transducer acts as a transmitter and the other as a receiver. The lower part of the dominant leg (defined as the leg used to stabilise oneself against a disturbance to standing balance) was immobilized and the proper leg angle set by a positioning aid. The Sahara device measures broadband ultrasound attenuation (BUA) (dB/MHz) and speed of sound with the one measurement (SOS) (m/s) at a fixed region in the mid-calcaneus, and combines the BUA and SOS into a single parameter, the quantitative ultrasound index (QUI): QUI = 0.41 x (BUA + SOS) – 571. Quality assurance was performed daily by calibrating the device on a dedicated phantom supplied by the manufacturer. The coefficient of variation (CV) for QUS measurements was 1%.

Statistics

Student *t*-tests were used for comparisons of means. The ambient temperature was found to significantly affect all QUS readings ($r = -0.06$ to -0.07, $p=0.01$-0.03). To adjust for this, ambient temperature was regressed on each of the QUS parameters and residual values were then calculated for each QUS parameter and used in the analysis (229). Linear regression techniques were used to explore the possible relationships between fitness measures and BMI, and the three QUS parameters, with standardised (beta) coefficients reported to allow direct comparisons. Multivariable results were age and BMI adjusted for possible confounding by these factors. Furthermore, each childhood measure was adjusted for the corresponding adult

measure (i.e. childhood PWC_{170} adjusted for adult PWC_{170}, childhood BMI adjusted for adult BMI). Models were also constructed containing the three dependant variables (QUS measures), each fitness variable (or BMI), sex and age, and their interaction term (fitness x sex, fitness x age, BMI x sex, BMI x age). Statistical significance was determined based on the *P* value for the interaction term. We also report partial R^2 (coefficient of partial determination) which measures the (square of the) mutual relationship between two variables when other variables are held constant. The partial R^2 allows us to directly estimate the proportion of unexplained variation of QUS that becomes explained with the addition of fitness or BMI to the model. A *p*-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 9.2 for windows (StataCorp LP).

6.3 Results

A sample of 1,434 participants was measured in 1985 as part of the ASHFS, and had follow-up measurements taken approximately 20 years later. Demographic and study factors of both participants in the current study (participants), and those for whom we did not obtain QUS data or who were lost to follow-up (lost to follow-up) are presented in Table 6.1. As children, participants were significantly older than those lost to follow-up and as such, were significantly taller, had a slightly quicker 1.6 km run time and a greater standing long jump. Male participants also had a slightly lower BMI and higher PWC_{170} than males lost to follow-up, while female participants had a one-tenth of a second quicker 50 m sprint time compared to females lost to follow-up.

There was a significant interaction between sex and the fitness measures (p=0.02-0.20), except for leg strength. As such, the results for males and females are

presented separately (Table 6.2). In females, there was a beneficial relationship between the 1.6 kilometre run and 50 meter sprint time and all QUS parameters, with the exception of 50 m sprint and BUA, with 1% of the variation in adult bone mass explained by the childhood 1.6 km run and 50 m sprint time. Similarly, in females, childhood standing long jump was positively associated with QUI and SOS, however this relationship did not persist after adjustment for adult ability. In males, none of the childhood fitness measures were predictive of adult QUS parameters.

Table 6.1. Characteristics of study participants*

	Males		Females	
	Participants (n=691)	Lost to follow-up (n=3616)	Participants (n=743)	Lost to follow-up (n=3448)
Childhood measures				
Age, years	11.2 ± 2.5	10.9 ± 2.6[a]	11.1 ± 2.6	10.8 ± 2.5[a]
Height, cm	148.4 ± 16.0	146.4 ± 16.3[b]	146.2 ± 14.1	144.6 ± 14.5[b]
Weight, kg	40.1 ± 12.0	40.1 ± 13.6	41.0 ± 13.5	39.3 ± 12.5
BMI (z scores), kg/m^2	-0.07 ± 0.90	0.01 ± 1.02[a]	-0.06 ± 0.89	0.01 ± 1.02
1.6km run, min:sec	8.5 ± 1.5	8.6 ± 1.7[a]	10.1 ± 1.7	10.3 ± 1.9[b]
50m sprint, sec	8.9 ± 1.0	9.0 ± 1.1	9.4 ± 1.0	9.5 ± 1.1[a]
Leg strength, kg	120 ± 60	114 ± 55	86 ± 35	83 ± 32
Standing long jump, cm	153 ± 31	150 ± 30[a]	138 ± 25	135 ± 25[b]
PWC_{170}, Watts/kg^{-1}	2.5 ± 0.5	2.4 ± 0.02[a]	1.9 ± 0.5	1.9 ± 0.5
Adult measures				
Age, years	31.3 ± 2.6		31.2 ± 2.6	
BMI, kg/m^2	26.5 ± 4.3		24.9 ± 5.0	
Leg strength, kg	180 ± 42		97 ± 30	
Standing long jump, cm	188 ± 26		134 ± 25	
PWC_{170}, Watts/kg^{-1}	2.4 ± 0.6		2.0 ± 0.5	
QUS measures				
QUI	106.4 ± 20.9		104.3 ± 19.6	
BUA (dB/MHz)	82.2 ± 19.1		77.6 ± 16.9	
SOS (m/s)	1570 ± 33.4		1570 ± 33.1	

*Means ± standard deviation. Subjects vs. lost to follow-up by Student's *t*-test [a]$P<0.05$ [b]$P<0.01$

Table 6.2. Relationship between childhood fitness measures and adult QUS measures in males and females*

	Males		Females	
	β (95% CI)†	β (95% CI)‡	β (95% CI)†	β (95% CI)‡
QUI				
1.6km run, min:sec	-0.0001 (-0.09, 0.09)	-	**-0.10 (-0.18, -0.02)**	-
50m sprint, sec	0.07 (-0.04, 0.17)	-	**-0.11 (-0.20, -0.01)**[a]	-
Leg strength, kg	0.01 (-0.23, 0.25)	0.05 (-0.22, 0.32)	0.08 (-0.09, 0.24)	0.03 (-0.16, 0.20
Standing long jump, cm	0.002 (-0.11, 0.11)	-0.11 (-0.24, 0.03)	**0.11 (0.02, 0.21)**[a]	0.07 (-0.04, 0.18
BUA(dB/MHz)				
1.6km run, min:sec	0.02 (-0.07, 0.11)	-	**-0.08 (-0.17, -0.003)**[a]	-
50m sprint, sec	0.06 (-0.04, 0.17)	-	-0.08 (-0.18, 0.02)	-
Leg strength, kg	0.06 (-0.16, 0.30)	0.05 (-0.21, 0.32)	0.06 (-0.08, 0.26)	0.05 (-0.13, 0.24
Standing long jump, cm	-0.03 (-0.14, 0.08)	-0.10 (-0.23, 0.04)	0.05 (-0.04, 0.14)	0.06 (-0.06, 0.17
SOS (m/s)				
1.6km run, min:sec	-0.01 (-0.11, 0.08)	-	**-0.10 (-0.18, -0.02)**[a]	-
50m sprint, sec	0.06 (-0.05, 0.17)	-	**-0.11 (-0.21, -0.01)**[a]	-
Leg strength, kg	-0.02 (-0.26, 0.21)	0.05 (-0.22, 0.32)	0.07 (-0.10, 0.23)	0.01 (-0.17, 0.18
Standing long jump, cm	0.02 (-0.09, 0.13)	-0.11 (-0.24, 0.03)	**0.14 (0.05, 0.23)**[b]	0.08 (-0.04, 0.19

*QUS = quantitative ultrasound. β = Standardised beta coefficients. †Adjusted for childhood age and BMI (
score). ‡Further adjusted for corresponding adulthood fitness measure. Bold denotes statistically significant result. [a]$P<0.05$ [b]$P<0.01$.

There was an interaction between age as a child and PWC_{170}, and all QUS parameters (all $p<0.01$) (Table 6.3). In nine years olds, childhood PWC_{170} was predictive of all QUS parameters independent of adult work capacity and explained 5-8% of the variation in adult bone mass. There was no sex interaction present in the nine year olds, with the strength of association being similar for both males and females (BUA: males: $\beta = 0.26$; females: $\beta = 0.31$, both $p<0.05$). There was however a sex-interaction present in the 12 year olds with PWC_{170} being positively associated with adult bone mass for females (BUA: $\beta = 0.25$, $p=0.045$), and negatively associated in males (BUA: $\beta = -0.23$, $p=0.06$). PWC_{170} at age 15 was not predictive of adult bone mass in either sex. The relationship for 9 and 12 year old females combined was QUI: $\beta = +0.25$, SOS; $\beta = +0.21$, BUA; $\beta = +0.30$, all $p<0.05$ (data not shown). The relationship between PWC_{170} and BUA in nine year olds is further illustrated in Figure 6.1 where there is a dose response relationship between quartiles of childhood PWC_{170} and adult BUA. Participants in the lowest quarter of childhood PWC_{170} had 15% lower adult BUA than those in the highest quarter.

Adjusting PWC_{170} for kilogram of lean body mass, rather than kilogram of body weight, did not substantially alter the strength of associations between childhood work capacity and adult bone mass.

Table 6.3. Relationship between childhood PWC_{170} (Watts/kg^{-1}) and adult QUS measures*

	Males and females (n=137)†	Males (n=65)‡	Females (n=68)‡	Males (n=73)‡	Females (n=66)‡
	9 year olds	12 year olds		15 year olds	
QUI	**0.28 (0.09, 0.48)**[b]	-0.22 (-0.48, 0.04)	0.22 (-0.02, 0.46)	0.08 (-0.09, 0.25)	-0.001 (-0.26, 0.26)
BUA (dB/MHz)	**0.32 (0.12, 0.51)**[b]	-0.24 (-0.50, 0.01)	**0.24 (0.01, 0.46)**[a]	0.06 (-0.11, 0.23)	0.08 (-0.19, 0.34)
SOS (m/s)	**0.25 (0.05, 0.45)**[b]	-0.20 (-0.45, 0.06)	0.19 (-0.06, 0.44)	0.09 (-0.08, 0.26)	-0.04 (-0.30, 0.21)

*PWC_{170} = physical work capacity at 170 beats/min (adjusted for body weight). QUS = quantitative ultrasound. Values are standardised beta coefficients (95% CIs). †Adjusted for sex, childhood BMI and adult PWC_{170}. ‡Adjusted for childhood BMI (z score) and adult PWC_{170}. Bold denotes statistically significant result. [a]$P<0.05$ [b]$P<0.01$.

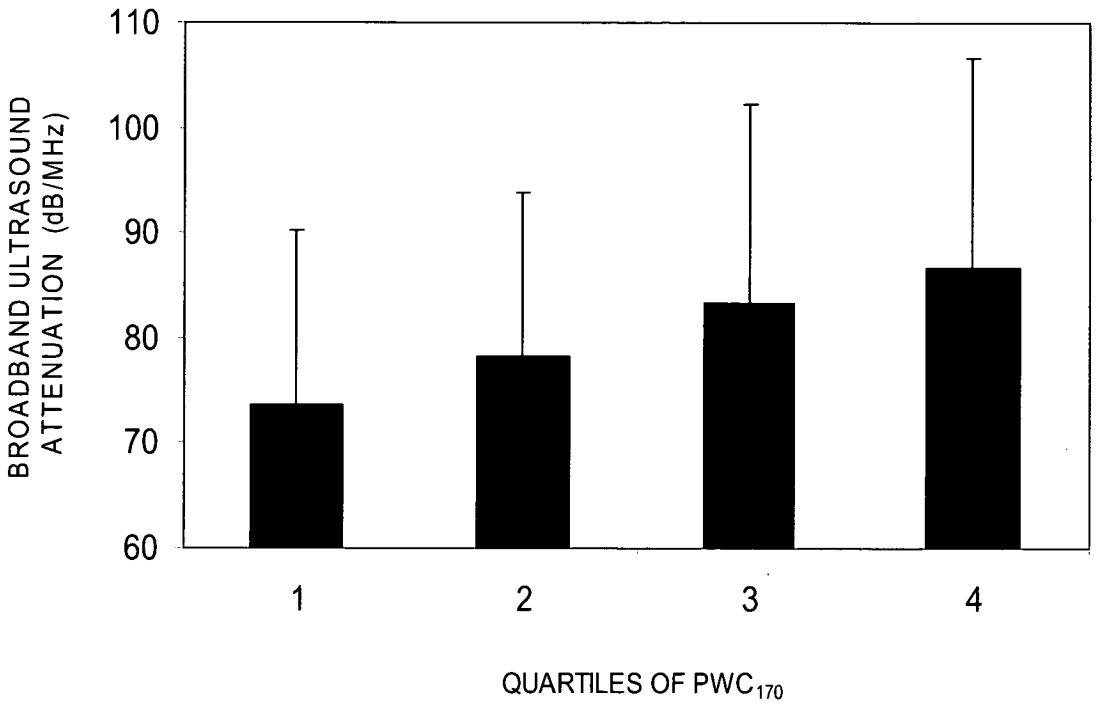

Figure 6.1. Association between quartiles of PWC_{170} and BUA in 9 yr olds.

Error bars represent standard deviations. There was a significant dose response relationship between quartiles of physical work capacity at 170 beats/min (Watts/kg^{-1}) and broadband ultrasound attenuation (dB/MHz) in 9 year olds. If the difference of 13 dB/MHz between the lowest and highest quartile of PWC_{170} persisted into older age; the relative risk of sustaining a fracture would be 1.7 times higher for the participants in the lowest PWC_{170} quartile compared to those in the highest.

There was also a significant interaction between sex and BMI (p=0.003-0.001) (Table 6.3). In males (but not females), BMI as a child was significantly associated with adult QUS parameters both before and after adjustment for adult BMI with 1-2% of the variation in adult bone mass of males explained by childhood BMI.

Table 6.3. Relationship between childhood BMI (z score) and adult QUS measures in males and females*

	Males		Females	
	β (95% CI)†	*P* value	β (95% CI)†	*P* value
QUI	**0.14 (0.06, 0.26)**	**0.002**	-0.01 (-0.11, 0.09)	0.83
BUA (dB/MHz)	**0.14 (0.06, 0.26)**	**0.001**	-0.03 (-0.13, 0.07)	0.52
SOS (m/s)	**0.14 (0.05, 0.25)**	**0.003**	0.0001 (-0.10, 0.10)	0.99

*BMI = body mass index. QUS = quantitative ultrasound. β = Standardised beta coefficients.

†Adjusted for age and adult BMI.

6.4 Discussion

This is the first long term inception cohort study to demonstrate that physical fitness in childhood is associated with bone mass in adulthood, independent of adult fitness. This is most true for females and pre or early pubertal children and confirms the evidence from retrospective and short term intervention studies that early childhood is an opportune stage of growth when the skeleton is most responsive to exercise. In addition, childhood BMI, was predictive of adult bone mass in males suggesting skeletal loading by body weight also has modest long term benefits.

Both genetic and environmental factors determine peak bone mass and physical performance (174,230). It is possible that common genetic factors explain the association between physical performance and bone accrual. However, it is likely that such gene effects track and by adjusting for adult fitness in our analysis, we minimise any shared genetic effects. The associations we report are therefore most likely to be due to environmental factors.

In regard to the three QUS measures, a meta-analysis of heel QUS and fracture (220) showed that QUI was most strongly related to fracture risk followed equally by BUA and SOS. This meta-analysis was limited to females however and included a range of QUS devices. Specifically looking at the fracture study that used the Sahara device (222), a 1 SD reduction in the three QUS variables resulted in relative risks for hip fracture ranging from 2.2 to 2.4. In three studies that also included males (221,223,224), BUA was most strongly related to fracture risk followed by SOS. QUI was not reported on in these studies. Thus, all three measures appear similar in terms of fracture risk. The most weight should be put on those measures which correlate with all three QUS variables.

A beneficial relationship was found between childhood PWC_{170} and adulthood QUS parameters in females. The magnitude of the regression coefficient indicates that a woman with a 1 SD higher PWC_{170} will have a 0.25 SD higher QUI. In terms of fracture risk, in older women it has been shown that each standard deviation reduction in QUI approximately doubles the relative risk for hip fracture, with slightly lower estimates for any fracture (221,223). Therefore, we estimate that for each $Watt/kg^{-1}$ decrease in PWC_{170}, fracture risk is increased by 25% (or 1.2-fold). Similarly, females in the lowest quartile of PWC_{170} would have a 1.4-fold increased risk of sustaining a fracture compared to females in the highest quartile of PWC_{170}.

The positive effect of childhood PWC_{170} on adult bone mass was strongest in both male and female nine year old children, thus lending support to the notion that a "window of opportunity" exists for the long term effects of exercise on bone accrual. The dose response association between quartiles of PWC_{170} and BUA in nine year olds is important for a number of reasons. Firstly, if the difference of 13 dB/MHz between the lowest and highest quartile of PWC_{170} persisted into older age, we estimate, based on the association between BUA and fracture (221,223) that the relative risk of sustaining a fracture would be 1.7 times higher for the participants in the lowest PWC_{170} quartile compared to those in the highest. Furthermore, children in the western world are becoming increasingly sedentary (231). This was illustrated by a much lower PWC_{170} in a more recently measured group of Australian children (232) compared to the 1985 ASHFS cohort. We could therefore speculate that today's children will have lower mean bone mass in adulthood, than is seen in the current adult population. As such, this study would support the need for physical activity with an emphasis on improving fitness through skeletal loading and this should constitute a

key element in the physical education curriculum and in general play, particularly in early childhood.

In females, the relationship between childhood standing long jump and adult bone mass was attenuated following adjustment for adult ability, suggesting that muscular power is only an important determinant of adult bone mass, if sustained into adulthood. Even so, this gives some insight into the debate concerning the relationship between muscle strength and bone mass (233-236) as despite the moderately high correlation between standing long jump and leg strength ($r = 0.52$), leg strength was not associated with any bone measures. This suggests that muscular power is a more important determinant of bone mass than strength alone.

A somewhat surprising finding was that childhood BMI in males, was predictive of their adult bone mass. Although a high BMI for age is strongly associated with fat mass, BMI in thinner children can be due to fat-free mass (237). Previous studies have demonstrated associations between body weight and fat mass, and bone mass, although lean mass tends to be the strongest predictor of bone mass accrual (179). Mechanisms underlying these associations are unclear, though a possible explanation is that more mass, whether it is adipose or lean tissue, elicits greater mechanical loading and thus stimulates osteogenesis. An important distinction should be made however between normal or "healthy" BMI and a BMI categorised as overweight or obese. The majority of children in our sample (~90%) were categorised as healthy weight according to the International Obesity Task Force definitions (238), thus it is largely variation within the normal range that is associated with bone mass. From our data, we estimate that those males in the lowest quartile of BMI would be at 1.7 fold increased risk for fracture compared to those in the highest, thus suggesting

that maintaining a healthy body weight in the upper part of the distribution throughout growth is good for bones.

Our data suggest sex differences in the effects of childhood exercise and body composition on adult bone mass in that exercise elicited most long term benefits in females, while for males, BMI was more important. This result is largely unexplained but is consistent with our earlier work in 8 year old children in which PWC_{170} was associated with bone mass in girls but not in boys (232). Similarly, a jumping exercise intervention was found to improve skeletal status in girls (194) more so than in boys (183). A threshold effect is plausible, however, splitting the boys at the mean of the fitness measures for girls' revealed opposite associations than would have been expected if a threshold effect existed. Males with performances below the female mean had positive associations with QUS measures, that is, the slower the 1.6 km run, the higher the adult bone measure, while males with performances above the female mean, were seen to have trends towards beneficial associations with adult bone mass (1.6 km run: $\beta = -0.08$ to -0.11, p=0.02-0.10; PWC_{170}: $\beta = +0.12$ to $+0.13$, p=0.08-0.10). It should be reiterated however, that the associations for PWC_{170} in nine year olds and adult QUS measures were similar for both males and females suggesting the differences became more apparent during puberty possibly due to sex hormone effects.

The current study has a number of potential limitations. Firstly, we were unable to adjust for adult 50 m sprint or 1.6 km run time and are therefore unable to conclude if these measures in childhood predicted adult bone mass independent of adult fitness. However, adjusting for adult PWC_{170}, a surrogate measure of endurance fitness only slightly attenuated the relationship between 1.6 km run and QUI and SOS, and did not alter the association for BUA. Secondly, the low response rate may

have introduced bias. However, the differences in childhood measures between participants and those lost to follow-up were minor (e.g. the 1.6 km run was on average 0.1 second quicker in male responders and on average 0.2 seconds quicker in female responders) and could largely be attributed to the age disparity. Likewise, this was statistically significant given the very large sample size but it is unlikely that such a small difference could be regarded as clinically significant or affect the results and their generalisability. We acknowledge there is still a potential for bias based on loss to follow up but this seems to be low in magnitude. In addition, such a bias towards "fitter subjects" does not automatically imply our results can not be generalized. In the previous chapter, Miettinen's (171) three key criteria for generalizability were described, all of which are met by this study. In a sensitivity analysis to determine if the less fit subjects show a similar relationship, we ran the following model for nine year olds who had a PWC_{170} below the group mean for nine year olds (<2.13 $Watts.kg^{-1}$) (n=60):

$$QUS_{9\text{-}yr\ olds\,j} = \beta_0 + \beta_1 * PWC_{170ASHFS\,j} + \beta_2 * PWC_{170adult\,j} + \beta_3 * BMI_{ASHFS\,j} + \beta_4 * sex_j + \varepsilon_j$$

Our results remained consistent and even somewhat stronger (β = 0.42, p=0.002), indicating that if anything, the loss of the "less fit" participants may have led to a weakening of the association. Thirdly, we did not have DXA measured BMD; however QUS predicts fractures, the critical end-point, similar to DXA. Furthermore, given this study was conducted across Australia, use of a portable QUS machine eliminated inter-machine variability which would have been a major problem had we used DXA. Similarly, although the use of QUS is justified through its relationship with fracture, there have been no studies showing QUS predicts fracture in the age range of the current study (mean age 31). However, no bone measures have been shown to predict fracture in this age range due to the rarity of fracture. Heel QUS has

been shown to predict fractures in many studies in later life and we have recently shown that it can discriminate adolescents who have fractured from those who have not (239). Thus, it would not be unreasonable to infer that QUS is a valid measure of fracture risk throughout the entire lifespan. Fourthly, we did not have QUS measurements at baseline. However, it is well established that weight-bearing exercise has positive effects on bone mass in childhood; the question we aimed to answer was whether childhood exercise confers lasting skeletal benefits. Lastly, we did not have measures of maturation status (i.e. Tanner stage) thus we are unable to draw conclusions regarding the effects of exercise at specific pubertal stages, although the literature suggests that the majority of nine year olds would be in Tanner stage 1 or 2, that is pre or early peripubertal (240). Furthermore, in many of our previous studies in children adjustment for age gives very similar results to pubertal stage (241) but our conclusions can only be based on age. Similarly, the fitness measures were not repeated in the same children during puberty so we can only infer that the effect is strongest in early pubertal children by comparing associations in different age groups.

In conclusion, this is the first prospective study to demonstrate that childhood fitness levels, particularly in females and in the pre or early pubertal years, are predictive of adult skeletal status as measured by QUS, explaining up to 8% of the variation in adult bone mass. Furthermore, childhood BMI in males was predictive of all adult QUS parameters. These results suggest that interventions aimed at increasing fitness through skeletal loading in early childhood leads to an increase in peak bone mass independent of current fitness or body mass index

CHAPTER 7: CAN BONE DENSITY ASSESSED BY DXA AT AGE 8 PREDICT FRACTURE RISK IN MALES AND FEMALES DURING PUBERTY? AN EIGHT YEAR PROSPECTIVE STUDY

7.1 Introduction

Fracture incidence is bimodal with a peak in adolescence and a peak in the elderly (82). Fractures in people aged under 50 years out number those due to osteoporosis by a factor of three (83). Large epidemiological studies have found 42-51% of boys and 27-40% of girls will have suffered at least one fracture during growth (242-244). Annual fracture rates are in the order of 57-85 per 10,000 for boys and 29-34 per 10000 for girls.

Forearm fractures are the most common fracture in childhood, representing 30% of all fractures (242). What's more, the incidence of childhood forearm fractures has appeared to increase over time. Khosla (245) found fractures increased between 1969-1971 and 1989-1991 and then levelled off into 1999-2001, an overall increase of 32% in males and 56% in females. Similarly, between 1950 and 1979 Ladin (242) documented an increase in distal forearm fracture of 35% in boys and 60% in females, with a subsequent study (243) showing no further increase in boys but a 31% increase in girls between 1975-1979 and 1992-1994. In a Danish population fracture rates increased 5% in boys and 33% in girls between 1975-1979 and 1985 (246). Possible reasons for the increase in fracture rates over time may be increased physical activity, decreased bone acquisition or both. Similarly, poor nutrition (i.e. inadequate intake of dietary calcium, milk avoidance and excessive consumption of carbonated beverages) and increasing obesity prevalence may have played a role (247).

In Australia, a high incidence of distal forearm fracture is observed in the 5 to 9 and 10 to 14 year age groups, and was associated with male patients more so than female patients (248), as shown in Figure 7.1. These data however are based only on those fractures requiring admission to hospital. In the United States it was estimated that 20% of all distal forearm fractures require hospitalization (249) with estimates in

Australia of the direct cost of managing this type of fracture on an in-patient basis being almost eight times higher than the cost of management as an outpatient. Nevertheless, as is described in the following paragraph, cost is only one of the consequences associated with fractures in children.

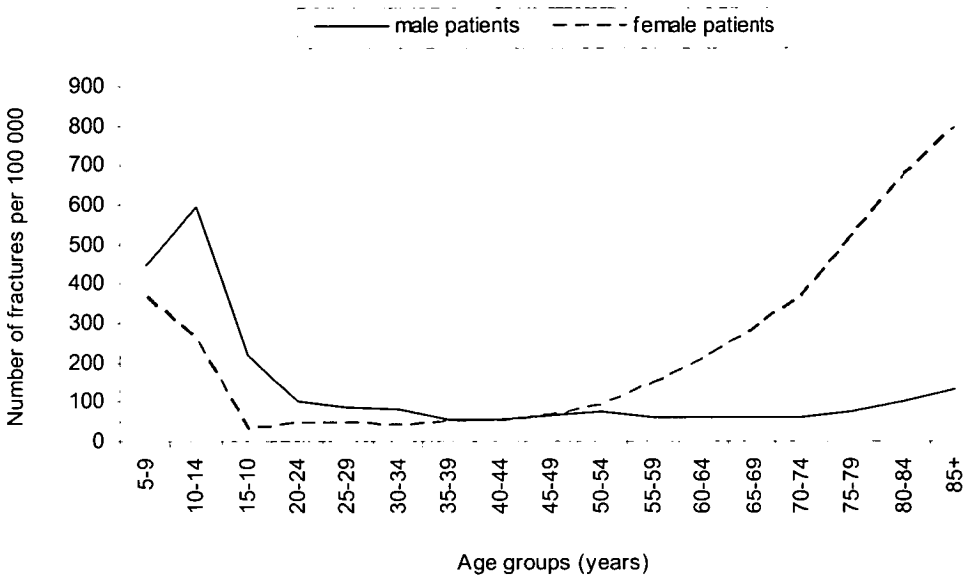

Figure 7.1. Age and gender specific incidence of distal forearm fracture admitted to hospital in Australia in 1997. Adapted from Wigg *et al.*, 2003 (248)

Owing to their high incidence, wrist and forearm fractures are the prime reason for hospitalisation in Australian children aged 10-14 and the third highest reason in children aged 5-9 (250). As well as their high incidence, significant consequences are associated with childhood fractures. As previously mentioned, there is the cost and hospitalisation, but also immobilisation of the limb, missed school days, activity restricted days (14 and 26 days for arm and leg fractures respectively) (251,252), developmental sequelae (253) and possibly osteoarthritis if the fracture is intra-articular (254). Complications from childhood fractures can also include

malalignment of the fractured bone, limb overgrowth (255) and acute compartment syndrome (256). Despite the high occurrence and aforementioned consequences, the causes of these fractures have been much less studied than fractures in later life.

It has generally been thought that childhood fractures are a normal event and reflect the frequency of falls and other injuries experienced during childhood. However one line of thought has been that there is a period of dissociation and therefore weakness due to a delay in bone mineralization relative to bone growth (248). Indeed, growth in size precedes increase in bone mass with peak velocity in BMC occurring approximately six months later than peak height velocity (257). What's more, Faulkner *et al* (257) found a decline in size-corrected aBMD coincided with peak adolescent fracture incidence in both boys and girls. There is mounting evidence however, that fractures in childhood are related to underlying skeletal fragility.

A number of case control and cross-sectional studies have suggested bone mineral density (BMD) like in older people, is also a risk factor for childhood fractures especially those involving the upper limb (241,244,258-261). Clark *et al* conducted a meta-analysis (258) of eight case-control studies of DXA measured bone mass and fractures in children aged <16 years. A total of 630 fractures and 1124 control children were included. The results showed the pooled standardized mean difference (SMD) for bone mass in children with and without fractures, was –0.32 (95% CIs: –0.43 to –0.21). An additional analysis of three studies (259,262,263) that presented data for children with wrist and forearm fractures showed a similar association to that observed with the main analysis: SMD = –0.25 (95% CIs: –0.40 to –0.10). The methodological quality of studies included in the meta-analysis was variable, with potential for bias and confounding. Similarly, in all studies, bone mass

was measured after the fracture with the time delay ranging from 12 hours to >1 year. Thus it is possible a reduction in bone mass followed the fracture. Goulding *et al* (260) found persistent low bone mass in girls who had fractured 4 years earlier indicating long term low bone mass, reducing the likelihood of reverse causality.

Three prospective studies in children (260,264,265) have confirmed the association for bone mass and total fracture incidence, but only one has specifically reported on upper limb fractures. Goulding *et al* (260) followed two cohorts of girls, aged 3-15 years, over four years. Group 1 had recently broken a forearm and group 2 were fracture free. In relation to bone mass, low total body aBMD doubled the risk of a new fracture at any site and specifically at the distal radius/ulna, while low spine BMAD significantly increased risk of a fracture at any site but not at the distal radius. The wide age range in this cohort combined with the major effect of puberty on bone size may have altered the apparent association between bone mass and fracture, resulting in a marked weakening of fracture prediction over time. In a much larger cohort (264) of 6000 children aged 9.9 years, fracture risk had only a weak inverse relationship to total body BMD and estimated volumetric BMD of the humerus (OR per SD decrease = 1.12 and 1.28 respectively). BMC was more strongly related to fracture risk when adjusted for bone area, height and weight (OR per SD decrease = 1.89) indicating children who fractured tended to have a smaller skeleton relative to their own body size. The third study (265) evolved from a randomised controlled trial of calcium enriched foods. 125 girls were measured at 1, 3.5 and 8.5 years of age. Bone densitometry was performed and fractures were recorded at each visit. Compared to the girls who had not fractured, BMC gain in the girls who had fractured was decreased by 8% (spine and hip) to 12% (radius). However, with the exception of

radius diaphysis and spine bone area (BA), BMAD and BA was not significantly different between groups.

A number of studies have implicated body weight or fat as a predictor of fracture in children (259,260,263). Skaggs *et al* (263) showed there was a tendency for girls (aged 4-15 yrs) who sustained a forearm fracture after minor trauma to be overweight. Similarly, in another study by Goulding *et al* (259), fracture patients aged 8-10 years weighed approximately 5 more kilograms than their age-matched counterparts (37.2 kg vs. 32.5 kg). What's more, overweight children have also been shown to have low bone mass for their body weight compared to their normal weight peers (266), a finding that was disputed in a later study where obesity was associated with a greater spine aBMD for height (267). Nevertheless, high body weight in 9 year old girls increased the risk of a new fracture 1.5-fold at any skeletal site, and 1.7-fold in the forearm (260). Some have suggested it may be time spent in front of the television and computer, rather than body fat per se. Ma *et al* (268) showed time spent television, computer, and video viewing was positively associated with wrist and forearm fracture risk in both sexes (OR 1.6/category, 95% CIs: 1.1-2.2) whereas days spent in light physical activity was seen to be protective.

Goulding *et al* has published two studies that have also implicated previous fracture (260,269). In the first study (260) they demonstrated that over a 4-year period, girls who had previously sustained a forearm fracture had a hazards ratio (HR) of 3.28 (95% CIs: 1.41-7.64) for a new fracture at any site. The subsequent risk for another forearm fracture was similar at 3.74 (95% CIs: 0.96-14.59). When previous fracture was combined singly with other risk factors (low spine BMAD, low total body aBMD, high body weight), the HR for a new fracture was in the order of 9.4 to 13.0. The second study (269), conducted in 601 members of a cohort studied between

birth and 18 years, found after the first fracture, there was a two-fold increased risk for a new fracture and after the second fracture, there was a 3-fold increased risk for new fracture. Reasons underlying this exacerbation of risk have not been elucidated but seem to indicate persistent low bone strength.

In summary, 42-51% of boys and 27-40% of girls will suffer at least one fracture during growth. The high incidence in childhood has been thought to be a result of a transient decrease in bone mineralisation relative to bone growth, however evidence now suggests that fractures in childhood are also a result of underlying skeletal fragility. Excess body weight and previous fracture have been identified as predictors of fracture in children.

Aim

The primary objective of this study was to prospectively examine the predictive value of a single DXA measurement at age 8 on fracture incidence (including those of the upper limb) between age 8 and 16 years. A secondary objective was to examine whether measures of body fat or previous fracture predicted subsequent fracture.

7.2 Materials and Methods

Subjects

In 1988, there were 6779 live births in Tasmania. Of these, 1498 were identified as being at higher risk of sudden infant death syndrome by previously published criteria (270) and were invited to take part in the Tasmanian Infants Health Study (TIHS) (Figure 7.2). In southern Tasmania, there were 735 births that met these criteria. Of these, mothers of 696 infants (95%) agreed to an in-hospital interview, and

the parents of 581 (80%) agreed to the 1 month follow-up. In 1996, 330 of the original cohort received bone densitometry testing at age 8 as previously reported (271). These children were then traced and asked to participate in a study on bone mass and fracture incidence in 2004-2005.

Fractures

Incident fractures were defined as any fracture that occurred subsequent to participating in the 1996 study and prior to taking part in the present study, and were ascertained by self-report with x-ray conformation (where possible). Information was collected on the age of the child when the fracture occurred, site, and circumstances of fracture. Upper limb fractures were defined as those involving the upper limb, not including the shoulder girdle. Trauma of the fracture was graded according to Landin trauma grading (242) as slight to moderate: a fall from less than 3 metres or equivalent velocity; and severe trauma: greater than 3 metres or equivalent velocity. Where a fall was not involved in fracture aetiology, a judgement was made as to the equivalent level of trauma.

Anthropometrics

In 1996, weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) and height was measured to the nearest 0.1cm (with shoes and socks removed) using a stadiometer. BMI was calculated and classified according to the Cole Criteria as normal, overweight or obese (238). The Cole Criteria is an internationally acceptable definition of childhood overweight and obesity, which provides age and sex specific, cut off points from 2-18 years. All children were

assumed to be prepubertal given the young mean age but this was not specifically assessed.

Bone mass

Bone mass was assessed in 1996 as previously reported (271) using dual energy x-ray absorptiometry at the total body, spine, and right femoral neck (Hologic QDR2000 densitometer, Waltham, MA). Bone mass was examined as bone mineral content (BMC), bone mineral density (BMD) and bone mineral apparent density [(BMAD) (g/cm^3)], which is an approximation of the volumetric density of bone and is calculated by dividing site-specific BMD by the square root of the area at that site (272). Body fat was also available from this scan. Precision estimates *in vivo* were not available in our subjects for ethical reasons. However, the longitudinal coefficient of variation for our machine during 1996 using daily measurements of a spine phantom was 0.54%.

Statistics

Student *t*-tests were used for comparisons of means. The longitudinal relationship between study factors and childhood fracture was analysed using Cox proportional hazards model for both total and upper limb fractures. Insufficient fractures were present for analysis of other fracture subgroups. Time was considered as months from clinic appointment in 1996 to first subsequent fracture (or to follow-up visit in 2004-5 if no fracture occurred). All results were adjusted for age at baseline, weight, height and sex. A *p*-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 9.0 for windows (StataCorp LP).

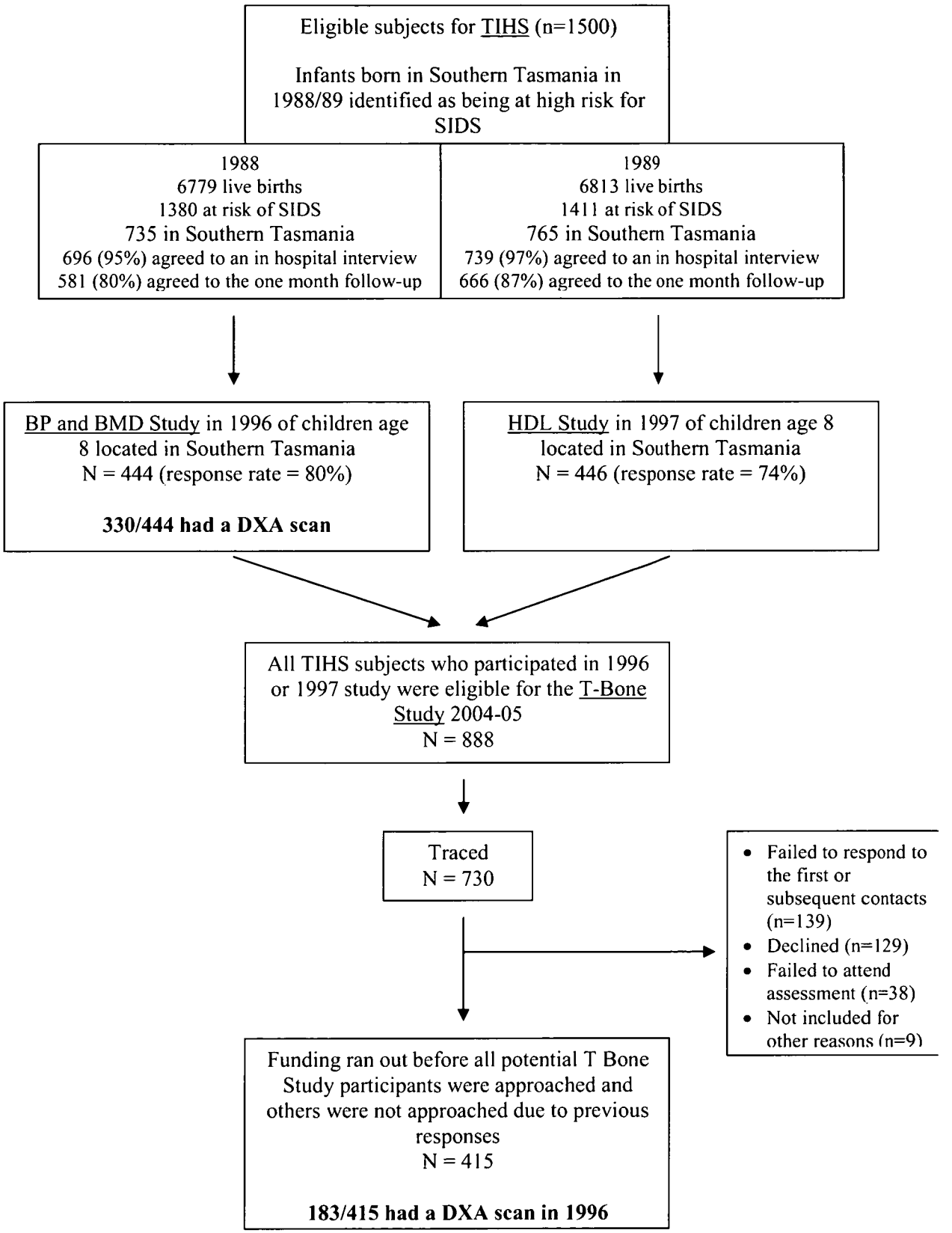

Figure 7.2. Flow chart of participation in the T Bone Study

7.3 Results

A total of 183 children were followed up in 2004-05 (mean age, 16.3 years, SD 0.4) representing approximately 1460 patient years (55% of those for whom bone densitometry was performed in 1996). Total first fractures numbered 63 with 53 being slight to moderate trauma and 10 high trauma. Forty three children sustained an upper limb fracture, of these 20 were forearm/wrist, 8 finger, 5 elbow, 5 hand, and 5 arm. Slight to moderate Landin trauma grade was recorded for 40 of the upper limb fractures, the remaining 3 were severe Landin grade. There were 12 lower limb fractures, 4 fractures of the nose, 2 clavicle fractures, 1 skull fracture, and 1 spine fracture. No significant differences between those studied and those lost to follow up were observed for explanatory factors or bone densitometry variables (Table 7.1). There were 16 of these subjects who had two fractures, 4 who had three fractures and one who had four fractures. Females tended to have a lower age at first upper limb fracture than males but this was not statistically significant (11.6 v 12.7 years, p=0.17). There was no difference in age for any fracture (data not shown).

Table 7.1. Characteristics of subjects at 8 years of age in study and those lost to follow up

	Subjects (n=183)	Lost to follow up (n=147)	*P* value
Male (%)	64	67	0.61
Age (years)	8.18 ± 0.33	8.23 ± 0.33	0.14
Height (cm)	127.76 ± 5.60	127.61± 5.91	0.81
Weight (kg)	28.05 ± 5.63	27.78 ± 5.57	0.67
Bone mineral content (g)			
Spine	20.08 ± 3.79	19.84 ± 4.15	0.59
Femoral neck	2.29 ± 0.57	2.27 ± 0.54	0.78
Total body	794.05 ± 162.05	794.01± 160.10	0.99
Bone mineral density (g/cm^2)			
Spine	0.60 ± 0.07	0.59 ± 0.07	0.30
Femoral neck	0.64 ± 0.08	0.63 ± 0.08	0.56
Total body	0.78 ± 0.05	0.77 ± 0.05	0.62
Bone mineral apparent density (g/cm^3)			
Spine	0.11 ± 0.01	0.10 ± 0.01	0.29
Femoral neck	0.34 ± 0.05	0.34 ± 0.05	0.61
Total body	0.02 ± <0.01	0.02 ± <0.01	0.70

Values are means ± standard deviations.

No differences in gender, age at densitometry, height, or weight were seen between the upper limb fracture group and those without upper limb fracture (Table 7.2). However, children who had an upper limb fracture had lower total body BMD and a trend for lower total body BMAD and spine BMC in unadjusted analysis over the 8 year follow up period (Table 7.2 and Figure 7.3). The association appeared continuous for total body BMC and BMD but appeared more threshold in nature for spine BMC and BMD, and total body BMAD. In multivariate analysis after adjustment for height, weight, sex and age at bone densitometry, upper limb fracture was predicted by (in rank order) total body BMC, spine BMC, total body BMD, total body BMAD and spine BMD, but not hip measurements (Table 7.3). Associations were similar in rank but consistently lower in magnitude when total fractures (including those of the upper limb) were analysed.

Figure 7.3 suggested a threshold effect rather than a continuous effect for spine sites and upper limb fracture risk. Analysis of the lowest quartile of bone densitometry versus the other three quartiles revealed hazards ratio for spine BMD of 2.05 (95%CI 1.01 – 4.20) and spine BMC 2.40 (95%CI 1.14 – 5.06), which were statistically weaker than when examined as a continuous variable with adjustment. However, the goodness of fit was similar for both the continuous and threshold models. Log likelihood for spine BMD for continuous and threshold models were similar ($p > 0.05$), indicating that neither model was superior.

Table 7.2. Characteristics of subjects at age 8 years with and without upper limb fractures and fractures at any site

	Upper limb		Any site	
	No fracture (n = 140)	Fracture (n = 43)	No fracture (n = 120)	Fracture (n = 63)
Male (%)	62	67	62	67
Age (years)	8.12 ± 0.35	8.03 ± 0.31	8.11 ± 0.35	8.07 ± 0.33
Height (cm)	127.8 ± 5.9	127.6 ± 4.4	127.8 ± 5.9	127.7 ± 5.0
Weight (kg)	27.9 ± 5.4	28.6 ± 6.0	28.1 ± 5.8	28.0 ± 5.4
Body fat (%)	21.3	22.8	21.5	21.8
Overwt/Obese (%)	17.9	25.6	20.8	17.5
Age at fracture (yrs)		12.3 ± 2.4		12.6 ± 2.4
Time to fracture (yrs)		4.3 ± 2.4		4.4 ± 2.4
BMC (g)				
Spine	20.37 ± 3.90	19.14 ± 3.25	20.5 ± 4.00	19.39 ± 3.24
Femoral neck	2.27 ± 0.56	2.33 ± 0.62	2.29 ± 0.55	2.28 ± 0.61
Total body	801.7 ± 163.3	769.1 ± 157.4	808.3 ± 167.4	767.0 ± 148.8
aBMD (g/cm^2)				
Spine	0.61 ± 0.07	0.59 ± 0.07	0.61 ± 0.07	0.60 ± 0.07
Femoral neck	0.64 ± 0.08	0.64 ±0.09	0.64 ± 0.08	0.64 ± 0.08
Total body	0.78 ± 0.05	0.76 ± 0.04*	0.78 ± 0.05	0.77 ± 0.04*
BMAD (g/cm^3)				
Spine	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Femoral neck	0.34 ± 0.05	0.34 ± 0.05	0.34 ± 0.05	0.34 ± 0.05
Total body	0.025 ± 0.0001	0.024 ± 0.0002	0.025 ± 0.002	0.024 ± 0.002

Values are means ± standard deviation. *fracture vs. corresponding control group ($P<0.05$).

Table 7.3. Bone mass at age 8 years and fracture prediction

	All fractures* HR/SD (95% CI)	Upper limb fracture* HR/SD (95% CI)
BMC (g)		
Spine	**1.56 (1.09, 2.24)**	**2.03 (1.30, 3.17)**
Femoral neck	0.98 (0.73, 1.32)	0.95 (0.67, 1.34)
Total body	**2.10 (1.34, 3.29)**	**2.48 (1.52, 4.06)**
BMD(g/cm^2)		
Spine	1.21 (0.88, 1.65)	**1.52 (1.05, 2.21)**
Femoral neck	0.97 (0.69, 1.36)	1.12 (0.76, 1.66)
Total body	**1.45 (1.08, 1.95)**	**1.75 (1.22, 2.52)**
BMAD (g/cm^3)		
Spine	1.01 (0.76, 1.35)	1.19 (0.85, 1.67)
Femoral neck	0.99 (0.75, 1.30)	1.15 (0.81, 1.63)
Total body	1.30 (0.91, 1.86)	**1.63 (1.05, 2.52)**

*Values are hazards ratios/SD reduction in bone mass (95% confidence intervals); adjusted for age, sex, height and weight. Bold denotes statistical significance.

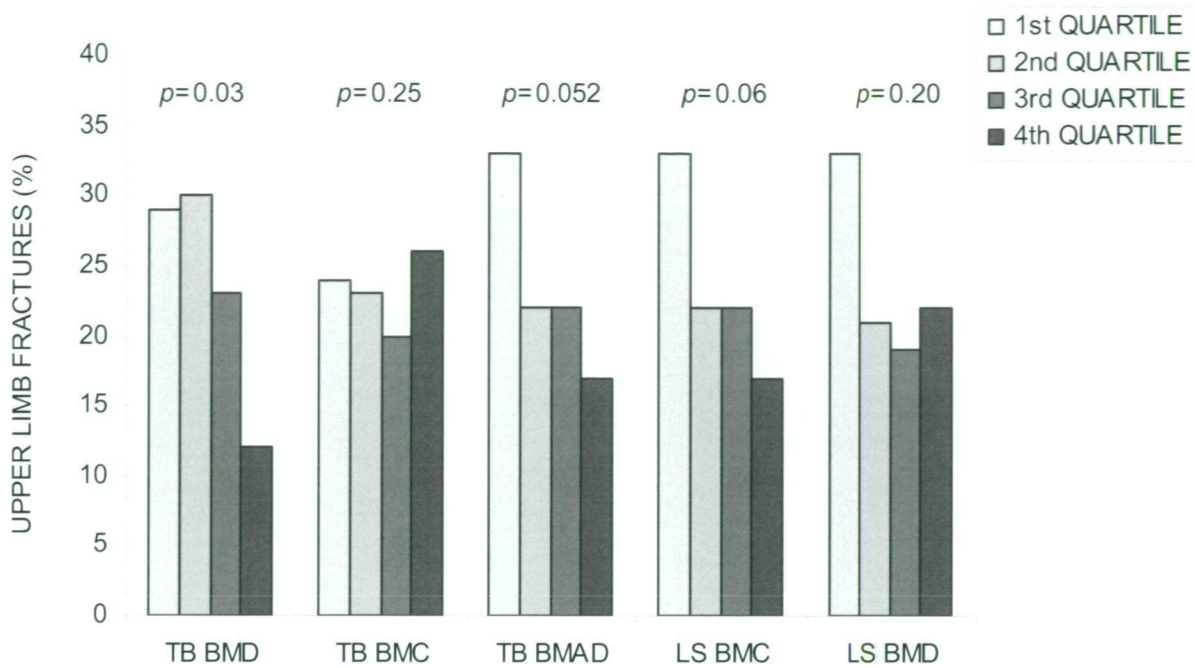

Figure 7.3. Percentage of children sustaining upper limb fractures between 8 and 16 by bone densitometry quartiles. Total body areal bone mineral density (TBBMD); total body bone mineral content (TBBMC); total body bone mineral apparent density (TBBMAD); spine bone mineral content (LSBMC); spine areal bone mineral density (LSBMD). This figure is suggestive of a continuous relationship between fracture incidence and total body BMD, and a threshold type relationship for spine BMD, spine BMC and total body BMAD.

There was no association between % body fat and fracture in unadjusted (Table 7.2) or adjusted analysis (data not shown). Category of overweight (normal, overweight, obese) did not predict total fractures in unadjusted analysi or adjusted analysis (data not shown) but there was trend for upper limb fracture (adjusted HR 0.53/category, p=0.08). A total of 18 children had fractures at baseline. However, fracture at baseline did not predict further fracture in this sample with a trend to a decrease in risk (HR 0.50, p=0.34).

7.4 Discussion

This is the first prospective study to report that a single bone densitometry scan at age eight can predict fracture risk in males and females (especially those involving the upper limb) during puberty. This ability for long term fracture prediction (an average of 4.3 years later) is important especially given the magnitude is similar to short term studies. This suggests that bone density tracks throughout adolescence, as has been documented in short-term studies so far (273) and that bone strength may remain relatively constant through this period despite the rapid change in bone size.

No single bone densitometry measure has consistently proven to be the best predictor of fracture risk in children. Total body BMC after adjustment for height, weight, age and sex had the strongest association with fracture risk, which is consistent with the previously published study of Clark *et al* (264) who reported an 89% increase in fracture risk for each SD decrease in adjusted BMC, but contrasts with the study by Goulding *et al* (260) who found BMD and BMAD but not BMC related inversely to fracture risk, and our previous case control study where BMC was not associated with fracture risk (241). Both the current study and the study by Clark *et al* included children of the same age while the latter two included a wide age range

of children, thus this discrepancy may be explained by the effect of a greater size variation on BMC leading to a weakening of fracture prediction. While there was size adjustment in these studies, the wide size variation still leaves open the possibility of residual confounding when the correlation between size and BMD is greater than the correlation between fracture and BMD. In the current study, the BMC measures performed better after size adjustment with weight accounting for the majority of this change. Given this, it may be that total body BMD is the best practical measure to assess fracture risk, as it requires no adjustment or manipulation.

We found weaker, yet significant, associations were present for spinal sites with a twofold increase in upper limb fracture risk for each SD decrease in adjusted BMC. Goulding *et al* (260) found a similar association for spinal BMAD and found low spinal BMAD predicts all fracture in children, but not forearm fracture alone. Ferrari *et al* (265) also showed spine BMC gain during puberty was decreased in the fracture group. Our finding contrast with our previous case control study where spine sites were consistently, but not significantly, stronger than total body sites for predicting wrist and forearm fracture (268). No associations were seen for hip measures in the current study. Our previous study was the only study to report an association between hip sites and upper limb fracture in children which is in contrast to adult studies which have reported that the hip is the best predictor of hip and total fractures (274). The reasons behind this discrepancy are unclear although most likely reflect the different fracture distribution in adults and children, different fracture aetiology, the measurement of hip bone density may be less reproducible in children as compared to adults and possibly sample size considerations.

A number of studies have implicated body weight or fat as a predictor of fracture in children (260,263) although some have suggested it may be television,

computer and video watching rather than body fat per se (268). The current study suggests that body fat may be a predictor of upper limb fracture only but this result did not reach statistical significance and requires confirmation in larger studies. Relevant to this, our sample was selected because they were at higher risk of SIDS. As a result, they were of lower mean birth weight than normal children as previously described (232). It is difficult to compare BMI distribution in different samples due to the rapid secular changes that are occurring in overweight children. In randomly selected fracture free controls studied from 1998-2002 from our location the prevalence of overweight/obesity was 29% overall but varied greatly by which fracture they were matched to (32% for hand fracture, 25% for forearm fracture and 38% for upper limb fracture) (268). This predominantly reflects the different age structure of the controls and the increase in true BMI with increasing age. In the current study, the prevalence of overweight/obesity according to the Cole criteria in fracture free subjects was 21% at age 8 in 1996 but increased to 29% at age 16 in 2004 consistent with this. Overall, this suggests that the BMI distributions are similar but may be slightly lower in this sample. This is somewhat surprising as low birth weight is a predictor of obesity in later life (275) but gives the current study marginally less power to examine body fat as predictor of fracture. Previous fracture was not a predictor of subsequent fracture in this sample. This most likely reflects sample size limitations with only 18 children having had a previous fracture.

This study has a number of potential limitations. While we had sufficient power for upper limb and total fractures, we could not examine the other fracture subtypes and would require much larger studies. Secondly, a sizeable percentage were lost to follow up raising the potential for bias, but reassuringly there were no statistically significant differences between the two groups, suggesting this is

unlikely. As we measured the children at age 8 and then age 16, we do not have valid data on peak height velocity. However, fracture incidence in our location does not provide strong support for this hypothesis with wide variations in peak fracture incidence that, with few exceptions do not coincide with the timing of peak height velocity in Australian children. Indeed, peak fracture incidence of forearm fractures in both sexes appears likely to be considerably before peak growth velocity (83). Furthermore, height velocity was not a predictor of upper limb fractures in our large fracture case control study (G Jones, unpublished).

In conclusion, measurement of bone mass at age eight by DXA is a good predictor of upper limb fracture risk during puberty. Although we did not measure true bone density, the constancy of fracture prediction following a single measure suggests bone strength remains relatively constant during puberty despite the large changes in bone size.

CHAPTER 8: TRACKING OF BONE MASS AND FACTORS THAT PREDICT CHANGE FROM CHILDHOOD TO ADOLESCENCE

8.1 Introduction

The 'peak' bone mass achieved in early adulthood is a major determinant of fracture risk later in life (174). Genetic factors explain a large proportion of peak bone mass with heritability estimates being as high as 60 – 85% in twin and family studies (276-279). Even before puberty there is a strong resemblance between mother-daughter bone traits as evidenced by heritability estimates in the order of 35% for spine and femoral BMC, BA, aBMD and BMAD between mothers and prepubertal daughters (273). Ferrari *et al* (265) also found a mean correlation of 0.38 between mother-daughter pairs for spine, hip and radius bone measures. Likewise, the daughters of women with osteoporosis had lower bone mineral content at the spine, femoral neck and femoral midshaft by 7, 5, and 3 percent, respectively, compared with normal premenopausal women (280). Such data implies bone mass is likely to track. That is, individuals maintain their ranked position in the distribution curve over time. Further evidence of tracking is the knowledge that genes associated with the normal variations in bone mass in the elderly are also related to variations in bone density in children (281-283). Tracking could have important implications for both early detection and future prediction of increased fracture risk.

Early evidence for tracking of bone mass was observed in early post menopausal women (284) in which DXA measures were correlated over a 12 year period. Ferrari *et al* (273) conducted the first analysis of tracking in children, demonstrating r values ranging from 0.76 to 0.91 for repeated DXA measures. His data were only over two years however and required confirmation over a longer period to determine if tracking remained during the entire period of bone growth. One such study was conducted as part of the Adelaide Nutrition Study (176). 56 boys and 52 girls had distal forearm bone width, mineral content and volumetric density

measured at age 11, 13, 15 and 17 years. From age 11 to 17 yrs, tracking coefficients for BMC, BW and volumetric BMD (vBMD) were 0.78, 0.85 and 0.35 respectively for males, and 0.69, 0.74 and 0.58 respectively for females. Similarly, of the children who were in the lowest and highest quintiles of vBMD as 11 year olds, the highest proportion remained in these respective quintiles at age 17. For example, of the girls who were in the highest quintile at age 11, 50% were still in the highest quintile at age 17.

Using computer tomography Loro *et al* (285) measured the densities and volume of bone in the axial and appendicular skeletons of 20 boys and 20 girls at Tanner stage II through to V. Cross-sectional area and cancellous bone densities of the vertebral bodies and the cross-sectional and cortical bone areas of the femur at the beginning of puberty accounted for 62-92% of the variation seen approximately 3 years later at sexual maturity. When the values for these traits were divided into quartiles, a linear relationship was observed for each quartile in both sexes. The plotted regression lines paralleled each other and did not over lap. Conversely, values for femoral cortical bone density in Tanner stage II did not predict those at sexual maturity and the regression lines for different quartiles intersected and were not parallel.

Ruff (286) analysed archived data from 10 boys and 10 girls that had been examined between 1941 and 1967 as part of the Denver Child Research Study. From radiographs taken at 6-month intervals from the age of 6 months to 17 years, the section modulus, a measure of bending/torsional strength, was derived from cortical and subperiosteal breadths at the femoral midshaft and the humerus. Tracking ranged from 0.29 to 0.69 over the ages 6 months to 16 years, with coefficients improving (0.54 to 0.83) when the age period 6 to 16 years was examined separately. Similar to

Loro's *et al* study, there was particularly poor tracking of femur strength in males, which was attributed to late and variable growth spurts in body size. Indeed, standardising for body size improved the tracking for the femur in males but not the humerus. More recently, Ferrari *et al* (265) followed girls from Tanner stage I to Tanner stage V and found the correlation between bone mineral content (BMC) measurements ranged from 0.54 (trochanter) to 0.81 (lumbar spine).

Whether this level of tracking is evident for spine and hip BMD has not been studied. Furthermore, it is not clear if the tracking of BMD is independent of physical growth, particularly given the known strong tracking of height. Additionally, while there's evidence of tracking of various bone traits in children, that's not to say that tracking cannot be altered by changing environmental factors, such as physical activity. But at this stage, there is no data specifically showing what factors can predict whether a child will deviate from their tracking trajectory. This is important given the foremost reason for identifying tracking in childhood is the notion that osteoporosis prevention could begin in early life. However if we're not clear what factors change the tracking trajectory, then interventions in childhood may be futile.

Assessment of bone mass/density is problematic in children. Bone densitometry measures include BMC which is unadjusted for bone size, or areal bone mineral density (aBMD) which is adjusted for the projected area of the region scanned but not its depth. As such, bone mineral apparent density (BMAD) (an estimate of volumetric bone mineral density) may help to minimise the effect of bone size (287,288). Nevertheless, we showed in the previous chapter that DXA measured aBMD is a good predictor of fracture risk during puberty (289) demonstrating its efficacy as a measure of bone strength in children and adolescence.

Aim

The aim of this eight year longitudinal study was to describe the tracking of bone mass from age 8 to age 16 years for BMC, aBMD and BMAD and determine if this tracking was independent of change in body size. A secondary aim was to determine what factors predicted whether children would *deviate positively,* that is improve in tertile or remain in the highest tertile, or *deviate negatively,* that is decrease in tertile or remain in the lowest tertile.

8.2 Materials and Methods

Subjects

The participants in this study were those as described in Chapter 7.

Clinical assessment

Weight and height were measured in 1996 and 2004-05 as described in Chapter 7. In 1996, all children were assumed to be prepubertal given the young mean age (8.1 years, range 7.3 to 8.8). At follow-up, pubertal status was self-assessed using drawings with an explanation of Tanner stages (290). Medication use, including inhaled corticosteroids (ICS), sunlight exposure and participation in competitive sports [both at age 8 (answered by a parent or guardian) and at age 16] was assessed by questionnaire. Data on breastfeeding and smoking during pregnancy was obtained in 1988. Breastfeeding was defined as either having ever being breastfed or never, which was reported by the mother approximately 1 month after giving birth. Physical work capacity was assessed by use of a bicycle ergometer (154) at both time points as previously described in Chapter 5 (232).

Bone mass and body composition assessment

Bone mass was assessed in the subjects at both time points using dual energy x-ray absorptiometry (DXA) at the lumbar spine, right total hip and total body (1996: QDR-2000 (Hologic, Waltham, MA) and 2004-05: Delphi (Hologic). Bone mass was examined as bone mineral content (BMC), areal bone mineral density (aBMD), and bone mineral apparent density [(BMAD) (g/cm^3)], which is an approximation of the volumetric density of bone and is calculated by dividing site-specific aBMD by the square root of the area at that site (287). The longitudinal coefficient of variation for our machine during 1996 and 2004-05 using daily measurements of a spine phantom was 0.54% and 0.34% respectively. Body composition (bone free lean mass and fat mass) was also available from the DXA scans.

Statistics

Student *t*-tests were used for comparisons of means. The relationship between DXA measures at age 8-yr and DXA measures at age 16-yr was analysed using Pearson and partial correlation coefficients. Results were examined both before and after simultaneous adjustment for change in weight (after excluding change in total body BMC) and change in height. The significance of the difference between correlation coefficients was examined using a *Z*-test. We also report partial R^2 (coefficient of partial determination) that estimates the proportion of unexplained variation of bone mass at age 16 that becomes explained when bone mass at age 8 is added to the model.

We also examined tracking by identifying the degree of downwards or upwards drift over the eight years from subjects originally (as 8 yr olds) in the highest or lowest tertiles respectively. Further to this, we used logistic regression analyses to

determine which factors predicted males and females would *deviate positively,* that is improve in tertile or remain in the highest tertile. Our reference group for this analysis was children who went down a tertile or remained in the lowest two tertiles. We used tertiles given our limited sample size. We did not have the power to include all independent covariates in the one multivariable model, therefore each outcome was modelled separately in multivariable models. Adjusted analyses are presented with confounders listed in footnotes underneath the results tables. Confounding factors included age, sex, height and weight. Where body composition was the outcome, the corresponding body composition measure was adjusted for (i.e. change in lean mass is adjusted for change in fat mass). Similarly, where "change" was the outcome, we adjusted for days of follow-up. Although fat mass in males, percent change in fat mass in females and change in absolute fat mass in both sexes were skewed, the model was not significantly improved by transforming these variables. Thus we have presented the results for the untransformed variables.

A *p*-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 9.0 for windows (StataCorp LP).

Results

All participants were 8 years old or younger at baseline (Table 8.1). At follow-up the mean age was 16 with the majority of subjects being in Tanner stage IV or V. As would be expected, height, weight, LM and FM increased substantially over the 8 year period. Fitness improved twofold, while sports participation was constant in males and increased somewhat in females. Approximately 10% of children used inhaled corticosteroids at age 8. Two thirds of children had been breastfed.

Table 8.1. Characteristics of participants*

	Males (n = 116)		Females (n = 67)	
	Mean age 8-yr	At follow-up	Mean age 8-yr	At follow-up
Age (years)	8.1 ± 0.32	16.4 ± 0.50	8.2 ± 0.38	16.4 ± 0.51
Age range (years)	7.3 – 8.7	15.5 – 17.6	7.3 – 8.8	15.7 – 17.4
Height (cm)	127.8 ± 5.9	174.7 ± 6.3	127.7 ± 5.1	162.2 ± 5.8
Weight (kg)	28.1 ± 5.8	71.0 ± 15.3	27.9 ± 5.4	62.6 ± 12.1
Lean mass (kg)	21.9 ± 2.7	56.1 ± 7.3	20.4 ± 2.5	42.2 ± 4.8
Fat mass (kg)	4.6 (3.7, 6.5)	12.5 (9.4, 20.1)	6.2 (4.5, 9.0)	20.0 (17.0, 27.3)
Sports participation (%)	73	68	58	79
PWC_{170} (Watts/kg^{-1})	1.18 ± 0.36	2.48 ± 0.67	1.00 ± 0.28	1.72 ± 0.37
PWC_{170} (Watts/kg LM^{-1})	1.52 ± 0.50	3.07 ± 0.72	1.39 ± 0.43	2.49 ± 0.37
ICS use (%)	10	13	11	15
Breastfed (%)	64		61	
Tanner stage	-	6, 68, 26	-	0, 55, 45
I - III, IV, V (%)				

*Values are mean ± standard deviation, except for fat mass where it is the median (interquartile range). ICS = inhaled corticosteroid.

From age 8 to 16, BMC approximately tripled at all sites (Table 8.2). aBMD increased ~60% at the spine, ~56% at the hip and ~35% for the total body. Spine BMAD increased 17% in males and 22% in females, with hip BMAD increasing 4% in males and 21% in females.

For all DXA measures there was a high level of tracking from childhood to adolescence, which was similar for both sexes before and after adjustment for change in height and weight (all $p<0.001$) (Table 8.3).

The tracking of hip and spine BMAD was not significantly different to the tracking of BMC and aBMD. The tracking coefficients of BMC and aBMD were comparable with but independent to those of height and weight over the same period (height: males: $r = 0.75$, females: $r = 0.79$; weight: males and females $r = 0.72$). Adjustment for height and weight at age 8 (either in separate models or in addition to change in height and weight) did not substantially change the coefficients (data not shown). Adjustment for change in lean mass did also not change the coefficients (data not shown). Examining tracking in those at Tanner stage V at follow-up (males: n=30; females: n=30) and those in Tanner stage IV or less (males: n=86; females: n=37) showed very similar coefficients for all DXA measures with no trend for tracking being higher or lower for differing Tanner stages. Furthermore, adjusting the results for Tanner stage at follow-up did not change the coefficients (data not shown).

Table 8.2. DXA measurements for males and females at mean age 8 and at follow-up.

	Males		Females	
	At mean age 8 yr	Follow-up	At mean age 8 yr	Follow-up
Spine				
BMC (g)	20.4 ± 3.67	62.4 ± 12.3	19.5 ± 3.94	55.8 ± 11.5
	(11.2 - 33.6)	(25.3 — 101)	(13.1 - 30.7)	(30.1 - 86.3)
aBMD (g/cm^2)	0.600 ± 0.072	0.964 ± 0.123	0.608 ± 0.070	0.977 ± 0.128
	(0.43 - 0.78)	(0.643 - 1.30)	(0.46 0.78)	(0.689 - 1.25)
BMAD (g/cm^3)	0.103 ± 0.013	0.120 ± 0.013	0.108 ± 0.012	0.132 ± 0.026
	(0.064 - 0.130)	(0.094 - 0.150)	(0.079 - 0.144)	(0.100 - 0.169)
Total hip				
BMC (g)	12.9 ± 3.03	44.3 ± 8.28	12.5 ± 3.27	32.4 ± 5.87
	(5.50 - 19.1)	(22.7 - 67.7)	(7.16 - 23.3)	(23.1 - 48.8)
aBMD (g/cm^2)	0.671 ± 0.077	1.042 ± 0.134	0.614 ± 0.064	0.962 ± 0.118
	(0.495 – 0.876)	(0.721 - 1.44)	(0.482 - 0.779)	(0.755 - 1.24)
BMAD (g/cm^3)	0.155 ± 0.018	0.160 ± 0.020	0.138 ± 0.012	0.166 ± 0.020
	(0.114 - 0.221)	(0.123 - 0.218)	(0.113 - 0.168)	(0.120 - 0.215)
Total body				
BMC (g)	807 ± 157	2313 ± 358	773 ± 169	2033 ± 300
	(272 - 1303)	(1294 - 3261)	(494 - 1317)	(1439 - 2781)
aBMD (g/cm^2)	0.783 ± 0.043	1.065 ± 0.099	0.763 ± 0.050	1.027 ± 0.093
	(0.66 - 0.89)	(0.823 - 1.30)	(0.67 - 0.92)	(0.813 - 1.32)

Values are mean ± standard deviation (range). aBMD = areal bone mineral density, BMC = bone mineral content, BMAD = bone mineral apparent density.

Table 8.3. Tracking of DXA measures from age 8 to age 16 yr in males and females.

	Males		Females	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Spine				
BMC (g)	0.74	0.74	0.81	0.80
aBMD (g/cm^2)	0.70	0.69	0.79	0.75
BMAD (g/cm^3)	0.62	0.61	0.71	0.69
Total hip				
BMC (g)	0.52	0.49	0.70	0.67
aBMD (g/cm^2)	0.66	0.65	0.75	0.70
BMAD (g/cm^3)	0.52	0.56	0.58	0.55
Total body				
BMC (g)	0.80	0.79	0.86	0.85
aBMD (g/cm^2)	0.64	0.64	0.64	0.60

Unadjusted values are Pearson correlation coefficient. Adjusted values are Partial correlation coefficients (R) for DXA measurements in prepubertal males and females (mean age 8 years) and adolescent males and females (mean age 16 years). *Adjusted for change in height and change in weight. All P-values <0.001

We also examined tracking by identifying the degree of downwards or upwards drift over the eight years from subjects originally (as 8 yr olds) in the highest or lowest tertiles respectively. In Figure 8.1 it can be seen that the majority of children who were in the lowest or highest tertile of DXA measured bone mass as eight year olds, remained in the lowest or highest tertile of DXA measured bone mass as adolescents. For spine and hip BMAD, approximately 90% of those in the lowest tertile at age 8 remained in the lowest two tertiles as adolescents.

LM at age 8, absolute and percentage increase in LM, PWC_{170} per kg/LM and increase in PWC_{170} increased the odds that males would *deviate positively* in regard to spine aBMD (Table 8.4). There was also a positive borderline association for increase in tertile and PWC_{170} per kg body weight and sports participation, particularly at age 8 to increase the odds, while increase in FM decreased the odds. For hip aBMD, increase in LM, increase in PWC_{170} and sports participation, particularly at both time points, increased the odds of *positive deviation*. Again, increase in FM was negatively associated. There was also a borderline significant association for ICS use at age 8 to decrease the odds of *positive deviation* and for having been breastfed to increase the odds.

For females, increase in LM and FM at age 8 increased the odds of *positive deviation* in spine aBMD (Table 8.5). PWC_{170} per kg/LM appeared to increase the odds but did not reach statistical significance and like males, being breastfed also appeared to be protective. Percent change in FM but not absolute change decreased the odds. For hip aBMD, increase in LM, FM at age 8 and PWC_{170} per kg/LM increased the odds of *positive deviation*, while percent increase in FM decreased the odds.

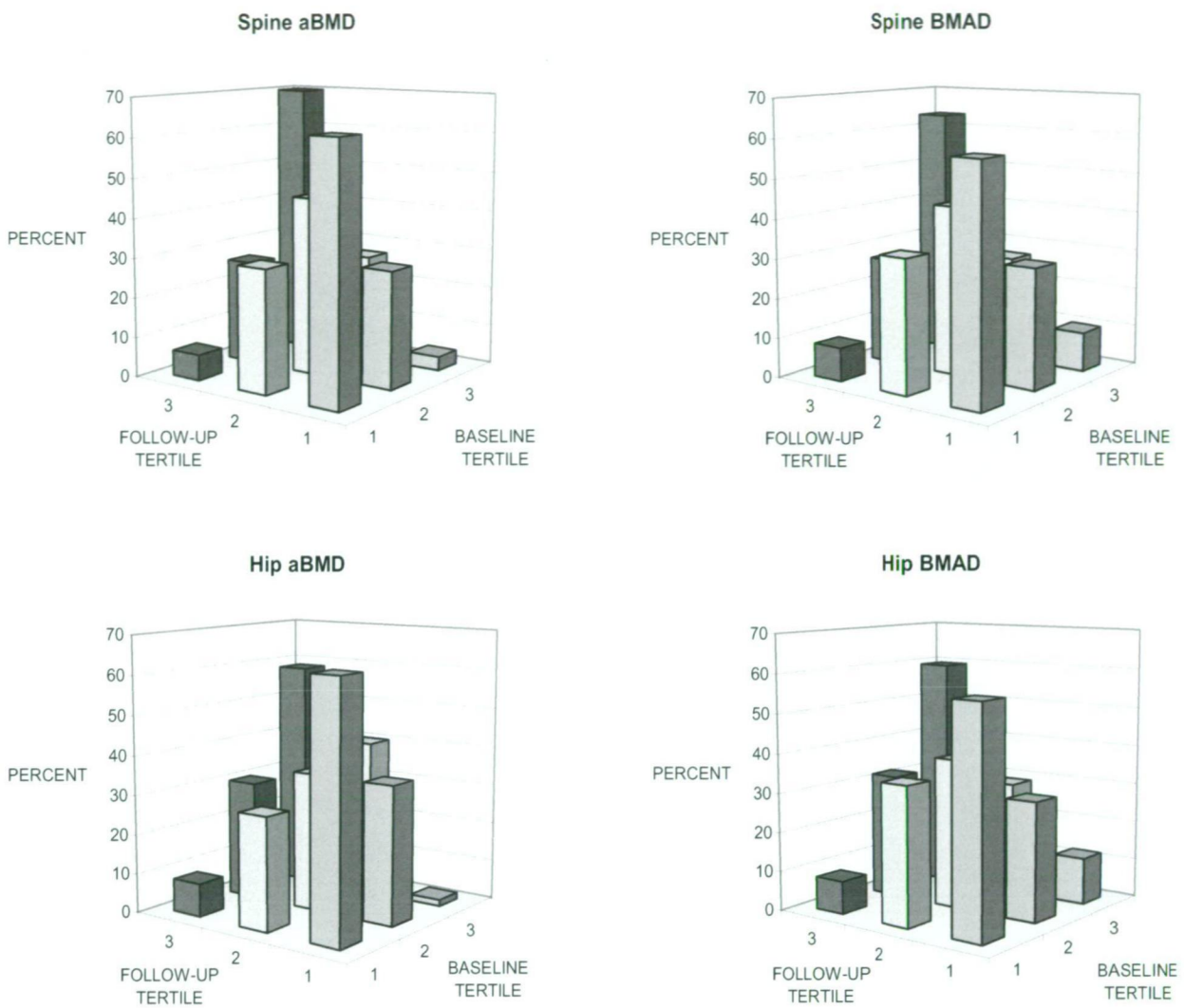

Figure 8.1. The proportion of subjects that were in the first (lowest), second and third (highest) tertile of DXA measurements for spine aBMD, spine BMAD, hip aBMD, and hip BMAD as eight year olds that were in the first (lowest), second and third (highest) tertile of DXA measurements as adolescents. The majority of children, who were in the lowest and highest DXA tertiles as eight year olds, remained in the lowest and highest DXA tertiles as adolescents

Table 8.4. Factors associated with increasing tertiles or remaining in the highest tertile of spine and hip aBMD from age 8 to age 16 for males

	Increase or highest tertile at both time points Vs. decrease or no change			
	Spine aBMD n=67 vs. n=49	*P*	Hip aBMD n=66 vs. n= 50	*P*
Breastfed (y/n)*	1.89 (0.77, 4.61)	0.16	1.46 (0.63, 3.41)	0.38
ICS use at age 8 (y/n)*	0.55 (0.13, 2.34)	0.42	0.24 (0.05, 1.19)	0.080
LM at age 8 (kg)†	**1.25 (1.03, 1.52)**	**0.023**	1.16 (0.97, 1.39)	0.11
Absolute change in LM (kg)†	**1.31 (1.16, 1.47)**	**<0.001**	**1.28 (1.14, 1.42)**	**<0.001**
Percent change in LM (%)†	**1.25 (1.09, 1.43)**	**0.002**	**1.30 (1.13, 1.50)**	**<0.001**
FM at age 8 (kg)†	1.07 (0.94, 1.21)	0.31	1.05 (0.93, 1.18)	0.46
Absolute change in FM (kg)†	**0.92 (0.86, 0.99)**	**0.023**	0.94 (0.88, 1.01)	0.068
Percent change in FM (%)†	**0.96 (0.93, 0.99)**	**0.005**	**0.97 (0.94, 1.00)**	**0.025**
PWC_{170} at age 8 (Watts/kg^{-1})*	3.78 (0.92, 15.6)	0.066	0.95 (0.29, 3.07)	0.93
PWC_{170} at age 8 (Watts/kg LM^{-1})*	**3.28 (1.03, 10.5)**	**0.045**	1.05 (0.40, 2.77)	0.92
Increase in PWC_{170} (per 10 Watts)‡	**1.02 (1.01, 1.04)**	**0.001**	**1.01 (1.00, 1.03)**	**0.015**
Participation in competitive sports‡				
Not at either time point	1.0		1.0	
Age 8 but not at age 16	5.22 (0.83, 32.8)	0.078	5.09 (0.77, 33.5)	0.091
Age 16 but not at age 8	4.80 (0.67, 34.6)	0.12	6.78 (0.89, 52.0)	0.065
Both time points	5.04 (0.85, 29.9)	0.075	**7.99 (1.27, 50.3)**	**0.027**

Values are odds ratios (95% confidence intervals). ICS = inhaled corticosteroid, LM = lean mass, FM = fat mass, PWC_{170} = physical work capacity at 170 beats/min. *Adjusted for age, height and weight. †Adjusted for days of follow-up and corresponding body composition measure (i.e. change in lean mass is adjusted for change in fat mass). ‡Adjusted for days of follow-up, change in height and change in weight. Bold denotes statistical significance.

Table 8.5. Factors associated with increasing tertiles or remaining in the highest tertiles of spine and hip aBMD from age 8 to age 16 for females

	Increase or highest tertile at both time points Vs. decrease or no change			
	Spine aBMD n=37 vs. n=30	*P*	Hip aBMD n=41 vs. n=26	*P*
Breastfed (y/n)*	2.29 (0.75, 6.96)	0.14	1.49 (0.47, 4.66)	0.50
ICS use at age 8 (y/n)*	1.85 (0.36, 9.40)	0.46	1.30 (0.25, 6.79)	0.76
LM at age 8 (kg)†	0.98 (0.75, 1.28)	0.90	0.99 (0.75, 1.30)	0.94
Absolute increase in LM (kg)†	1.25 (1.00, 1.55)	0.052	**1.36 (1.06, 1.73)**	**0.014**
Percent increase in LM (%)†	**1.23 (1.03, 1.47)**	**0.021**	**1.30 (1.07, 1.58)**	**0.007**
FM at age 8 (kg)†	**1.27 (1.03, 1.56)**	**0.026**	**1.30 (1.06, 1.60)**	**0.011**
Absolute increase in FM (kg)†	1.03 (0.93, 1.15)	0.58	1.04 (0.94, 1.17)	0.45
Percent increase in FM (%)†	**0.95 (0.90, 1.00)**	**0.042**	**0.94 (0.89, 0.99)**	**0.019**
PWC_{170} at age 8 (Watts/kg^{-1})*	1.49 (0.15, 14.9)	0.73	4.21 (0.41, 43.5)	0.23
PWC_{170} at age 8 (Watts/kg LM^{-1})*	2.37 (0.42, 13.4)	0.33	5.08 (0.81, 31.9)	0.083
Increase in PWC_{170} (per 10 Watts)‡	0.99 (0.96, 1.03)	0.69	0.99 (0.95, 1.03)	0.54
Participation in competitive sports‡				
Not at either time point	1.0		1.0	
Age 8 but not at age 16	0.19 (0.01, 2.63)	0.22	0.20 (0.01, 4.11)	0.30
Age 16 but not at age 8	0.36 (0.04, 3.44)	0.38	0.46 (0.03, 6.22)	0.56
Both time points	0.41 (0.05, 3.63)	0.42	1.31 (0.11, 15.4)	0.83

Values are odds ratios (95% confidence intervals). ICS = inhaled corticosteroid, LM = lean mass, FM = fat mass, PWC_{170} = physical work capacity at 170 beats/min. *Adjusted for age, height and weight. †Adjusted for days of follow-up and corresponding body composition measure (i.e. change in lean mass is adjusted for change in fat mass). ‡Adjusted for days of follow-up, change in height and change in weight. Bold denotes statistical significance.

When we examined which factors predicted children would *deviate negatively*, our results were not surprisingly the opposite of those presented above. For example, ICS use at age 8 and percent increase in FM increased the odds of *negative deviation*, while having being breast fed, increase in LM and PWC_{170} and sports participation in boys, decreased the odds.

We also analysed our data to determine which factors would predict subjects would remaining in the upper 50^{th} percentile vs. those who moved to the lower 50^{th} percentile and similarly for subjects remaining in the lower 50^{th} percentile vs those who moved to the upper 50^{th} percentile. We also repeated the presented analysis using quartiles and a method of Royston (291), instead of tertiles (data not shown). In all analyses, the odds of moving up or remaining in the top tertile/quartile/50^{th} percentile were increased by being breastfed, lean mass at age 8, change in lean mass and change in PWC_{170}, and decreased with ICS use and percent change in fat mass.

Breast feeding was not related to fitness or body composition and was therefore not a confounder of the relationship between these outcomes and altered tracking. Likewise, smoking during pregnancy and sunlight exposure at age 8 were not related to altered tracking of either spine or hip aBMD (data not shown). Adjusting for Tanner Stage at follow-up did not change the results.

There were no statistically significant differences between those included and those lost to follow up for bone mass or anthropometric variables (289).

Discussion

As far as we are aware, this is the first longitudinal study to examine the tracking of bone density at the hip, spine and total body from the prepubertal years to late adolescence in males and females. The results of this study confirm and extend

previous reports (176,265,285,286) and demonstrate that BMD and BMAD track strongly from the prepubertal years to late adolescence when peak bone mass is largely attained (175,176). Despite the strong tracking, a number of factors either were significantly associated with or had modest associations with altered tracking over this period.

These results are important for a number of reasons. Firstly, given bone mass tracks strongly and that the majority of children who are in a given tertile of bone mass at age 8 remained in that tertile in adolescence, this suggests that susceptibility to osteoporosis can be identified early in life. Thus, those who are low can be targeted for interventions such as physical activity which have their greatest impact in the prepubertal years (292) and at least some of this is maintained into adult life (293). The high heritability estimates for bone mass in mother prepubertal child pairs (273,294) suggests that at-risk children could also be identified through measurement of their parents. Lastly, the somewhat unexpected finding that bone mass tracks largely independently to height and weight suggests that bone development and linear growth are under largely separate mechanistic control.

The tracking coefficients were generally higher in females than males. This is somewhat unexpected as, at age 16, most boys will be approximately two years past their peak growth spurt, while girls will be approximately four years past their peak growth spurt (180).

Although the study wasn't adequately powered to identify predictors of altered tracking, a number of factors either were significantly associated with or had suggestive associations with altered tracking over this period. Of note, were the sex differences in the associations with body composition. For males, lean mass at age 8 was a predictor of changing tertiles of bone mass, while in females it was more so

their fat mass at age 8 that predicted future change. Greater absolute and percent increases in lean mass were associated with increasing odds of *positive deviation* with opposite associations for *negative deviation* of spine and hip aBMD. In contrast, girls who gained more percent fat mass, and boys who gained absolute or percent FM were less likely to move up or stay in the highest tertile and more likely to move down or stay in the lowest tertile of both spine and hip aBMD. The difference in significance between absolute and percentage fat mass in females suggests that the relationship is being driven by those with less fat mass at baseline.

Physical activity also appeared important. The greater the improvements in endurance fitness assessed by PWC_{170} over the eight year follow-up period, the more likely children were to *positively deviate*. In the same way, there was a trend for higher fitness at age 8 to lessen the likelihood of *negative deviation* of spine aBMD. For boys, participation in competitive sports at age 8 and during adolescence also increased the likelihood of *positive deviation* of hip aBMD. Sports participation was positively related to fitness (data not shown) but the associations with tracking were largely independent.

Inhaled corticosteroid (ICS) use at age 8 was associated with a 70% increase in the likelihood of males moving down or staying in the lowest tertile of hip aBMD. This result was predominantly driven by five boys on an ICS dose of 800 μg/day so it requires confirmation in larger samples. Additionally, adjustment for PWC_{170} but not sports participation attenuated the relationship between ICS use and altered tracking of hip aBMD, suggesting poorer fitness resulting from either disease or a direct effect of ICS on muscle function may also mediate this relationship. Being breastfed as a baby appeared to have long term benefits for spine aBMD, with breastfed children being half as likely to *deviate negatively* for spine aBMD, and twice as likely to

deviate positively compared to children that had not been breastfed. This is consistent with our previous study in which children who had been breastfed had higher bone mass at age 8 (295) and were also less likely to sustain a fracture (262), suggesting children who have been breastfed follow a different trajectory of bone accrual leading to long term protection.

The current study had a number of potential limitations. Firstly, this was not a representative sample of Tasmanian children as subjects were originally selected on the basis of being at high risk of sudden infant death syndrome. Consequently, this cohort is of a lower socioeconomic status than the general Tasmanian population. Nevertheless, the criteria for generalizability as stated by Miettinen (171) were all met by this study. Secondly, we were unable to assess bone mass at age 8 and at follow-up using the same densitometer. However, any measurement error that is likely to result from the use of two different machines would tend to weaken the strength of associations reported. Furthermore, it has been shown that Hologic densitometers are relatively interchangeable (296). Thirdly, a sizeable percentage were lost to follow up raising the potential for bias, but reassuringly and as reported in the previous chapter, there were no statistically significant differences between those included and those lost to follow up for bone mass or anthropometric variables (289) suggesting this is unlikely. Fourthly, we did not have measures of maturation status (i.e. Tanner stage) at baseline, however the literature suggests that the majority of eight year olds would be in Tanner stage 1 (240). We also did not perform blood samples at age 8 to assess endocrine factors that may elucidate why bone tracks independent of height and weight. Lastly, although we identified a number of factors associated with altered tracking, these analyses were not the primary aim of this investigation. It should

therefore be regarded as an exploratory analysis which is worthy of further investigation in larger studies.

In conclusion, DXA measures track moderately to strongly from childhood to adolescence. This was independent of linear growth and sex indicating bone development and physical growth are under largely separate mechanistic control. Body composition was the main predictor of altered tracking but environmental factors such as being breastfed, fitness, sports participation and ICS use also appear important.

CHAPTER 9: PEDOMETER DETERMINED AMBULATORY ACTIVITY AND BONE MASS: A POPULATION BASED LONGITUDINAL STUDY IN OLDER ADULTS

9.1 Introduction

It is frequently reported that maintaining weight bearing activity in later life may lessen age-related bone loss (297) and even reduce the risk of fractures (298-300). Walking is of particular interest as a strategy to maintain bone mass but the evidence to support it is conflicting in women and lacking in men. From a public health perspective, walking is a very easy behaviour to promote. It is popular with older adults and is often the most cited form of activity (301). Its accessible, can be easily incorporated into people's day, does not involve a cost or special equipment and is without adverse side-effects, not to mention the many other positive health outcomes that walking can bring about (302).

Case controls studies have generally shown physical activity, including walking, is associated with a reduced risk of hip fractures (303). Cooper *et al* (300) showed activities of daily living (including standing, walking, climbing stairs, carrying, housework, and gardening) were protective against hip fracture in men and women. However, when walking was examined on its own, the significant effect did not hold. Coupland *et al* (304) and Cummings *et al* (305) both found daily walking was associated with reduced odds of fracture in men and women, where as in Lau *et al*'s study (306) daily walking only had a beneficial effect in women and not men.

Several prospective studies have evaluated the association between physical activity and hip fracture risk. One of the earliest studies showed that being active for more than an hour a day could reduce the risk of hip fracture by 40-50% (307). The Study of Osteoporotic Fractures (SOF) (298) used a total physical activity score which included number of blocks walked and stairs climbed. They found higher levels of physical activity, household chores and fewer hours of sitting daily were associated with a 36% reduced risk for hip fracture. Specifically looking at walking, Cummings

et al showed women who walked regularly for exercise and women who spent 4 hr/day or more on their feet had a 30% reduced risk of hip fracture (299). In the Nurses Health Study (301) risk of hip fracture was lowered by 6% for each increase of three metabolic equivalent hours of activity per week (equivalent to 1 h/wk of walking at an average pace). Similarly, among women who did no other exercise, walking for at least 4 h/wk was associated with a 41% lower risk of hip fracture compared to women who walked less than 1 hr/wk. The evidence from such cohorts in men was less conclusive until recently, when Michaëlsson and colleagues published a study involving a cohort of 2,205 men followed for 35 years (308). The men were classified into three groups according to whether their level of physical activity was high, medium, or low. At the end of the follow-up, 8.4% of the men in the high physical activity group, 13.3% of the men in the medium physical activity group, and 20.5% of the men in the low physical activity group had suffered a hip fracture. Similalry, men who oftened cycled or walked for pleasure but did not participate in recreational sports or training, were less likely to sustain a hip fracture compared to sedentary individuals. Less data exists concerning physical activity and vertebral fractures. Two case control studies found positive effects from physical activity but neither was statistically significant (309,310). A third showed current walking or cycling more than 1/2 h/day was associated with a 20% reduced risk of vertebral deformity in women (311). In the SOF study (298), women who did moderate-to-vigorous exercise had a 33% reduction in vertebral fracture odds compared with inactive women. Total physical activity, household chores and sitting were not associated with vertebral fracture.

Despite the consistent findings of the aforementioned studies, a hypothesis-proving study (a randomized, prospective trial) with fracture as the end point should

be executed before we can truly say exercise reduces fracture risk. Such a study poses a formidable problem given the incidence of injurious falls is low. Therefore it is worthwhile looking for positive effects of exercise on surrogate end-points for fractures. Given bone mass is a major determinant of fracture risk (312), the association of physical activity and walking with fracture risk is likely to be due in part to effects on bone mineral density.

There have been several training studies looking at the effect of walking programs on bone mass. A meta-analysis published in 2002 (78) showed brisk walking, 30-45 min, 3 times a week for 7 to 24 months had a positive effect on postmenopausal women's spine BMD (weighted mean difference: 1.31, 95% CIs -0.03 to 2.65). The change in BMD in the training group was only about 1%. Conversely, five aerobic exercise interventions (313-317) had no effect on the hip. Of the five aerobic interventions, two were resistance training (316,317), two consisted primarily of weight bearing activity (313,314) and one was a mixture of both (315). Similarly, a more recent meta-analysis (81) of nine studies of walking only interventions in postmenopausal women (318-326), found walking had a small positive effect on lumbar BMD (effect size: 0.32) and no effect on the femur or the calcaneus. If we look at the two studies that included women older that 65 years, we see first, the net changes in femoral neck aBMD showed a trend in favour of the walking group at 2 years: 0.019 g/cm^2 (95% CIs: -0.0026, +0.041, p=0.056) (322) and secondly, change in femoral neck aBMD is related to the amount of walking completed (r=0.51, p=0.01) (318). Since the two aforementioned meta-analyses, two other RCTs have been published. The first engaged postmenopausal women in 15 or 30 weeks of supervised walking, 4.8 km/day, 4 days a week at either 67% or 85% of VO_{2max} (327). After 15 weeks of training the results showed BMD of the legs and

whole body increased in the high intensity group (n=13) compared to low intensity (n=12), and women in the high intensity group who trained for 30 weeks (n=16) had significantly higher BMD at the pelvis. The second RCT was a 48 week multi-component exercise program consisting of stretching, strength training, weight-bearing exercise and balance and posture training (328). BMD of the femoral neck and trochanter in the exercise group increased significantly but evidently the effects of individual program components, i.e. weight bearing exercise, can not be deciphered. From such studies it appears the greatest bone mass differential was observed between groups in which walking was done at 90% heart rate max (323,327) and in those studies that included older individuals (318,322).

The most recent meta-analysis examined eight trials of walking for the preservation of bone mineral density in postmenopausal women (329). Their results showed no significant change in BMD at the lumbar spine [weighted mean difference (WMD) (fixed-effect) 0.007 g/cm^2 (95% CI: -0.001 to 0.016; P=0.09)]. Five trials had BMD data at the femoral neck with the results showing a positive effect of walking on BMD at this site [WMD (random-effects) 0.014 g/cm^2 (95% CI: 0.000 to 0.028; P=0.05). Insufficient data were available for meta-analysis of the total hip site.

The aforementioned training studies were limited by small sample sizes (some even inadequate), recruitment of volunteers and in the 2005 meta-analysis, inclusion of some quasi experimental designs (i.e. lack of control group). There was also a vast range of prescribed walking durations, frequencies and intensities, as were there methods to measure BMD (single-photon absorptiometry, dual-photon absorptiometry, computer tomography and dual energy x-ray absorptiometry). Finally, the majority of walking interventions were unsupervised with self-reports of the amount of training completed. For all these reasons, the true effects of walking on

bone mass may have been masked. Similarly, given long-term adherence to organised exercise regimes is generally low, the promotion of habitual physical activity, may precede greater compliance, and therefore be a lasting strategy to prevent bone loss. Additionally, home-based daily physical activity would appear to be an exceedingly cost-effective approach.

Observation studies have examined habitual walking and bone mass (330-332). Life long walking habits have been shown to be positively related to women's bone density (331). Specifically, duration of walking was associated with BMD at the spine and total body when comparing women walking less than one mile per week to those women walking more than 7.5 miles per week. In a longitudinal study spanning 5.6 years, Puntila *et al* (332) found those women who reported participating in regular leisure time walking or jogging had less annual changes in spine bone mass compared to women who did not participate in such activity, however no differences were seen for the femoral neck.

The majority of research on walking, and even to an extent, physical activity and bone mass has been conducted in post menopausal women. In older men, cross sectional (333-336) and retrospective (310,337,338) studies have generally shown active men have higher BMD than less active men and that physical inactivity, like for women, is a risk factor for osteoporosis (339). Longitudinally, the results are a little more conflicting. Bakhireva and colleagues (340) found physical inactivity predicted bone loss whereas in the Framingham study (341) bone loss was not affected by physical activity.

Only two studies have looked at walking in men. The first, in 43 subjects, ranging in ages from 26-51, Hutchinson *et al* found the number of daily walking steps was not related to calcaneal bone mass (79). In this study, steps were measured using

a stepmeter, which participants were instructed to only wear during walking activities, such as gardening, golf, exercise walking etc, as such, steps from high loading activities did not contribute to recordings. Indeed, self-reported high loading activities were related to bone mass in this population. Huuskonen *et al* (80) conducted a RCT of aerobic exercise in 50-60 year old Finnish men. The intervention consisted of brisk walking starting at 30-45 minutes three times a week, increasing to 60 minutes 5 times a week after three months. No measurable effect on aBMD was observed between groups. Lack of effect may be because the men performed the training program on their own and the reference group were advised to make their own choice whether or not to partake in activity. Nevertheless, the intervention group did increase their aerobic threshold compared to the control group suggesting internal validity. Lastly, both Husskonen *et al* and Hutchinson *et al* examined walking in men younger than 60 years. Given 15-30% of all men will suffer an osteoporosis related fracture (7,8,342) and fracture incidence rises exponentially after age 65 (343), it is imperative studies include older men to identify cost-effective means of preserving bone mass in those most at risk.

As highlighted, observational studies examining habitual walking and bone mass, have used questionnaires to assess quantity of walking. The limitations of questionnaires to measure physical activity are well documented (142-144) and include recall bias, floor effects, and a variety of scoring procedures and output units. Accelerometers and pedometers offer an objective measure of physical activity and are not subject to recall bias. Accelerometers can detect volume of movement and thereby infer time in bouts of activity at various intensities. Although they are a valuable tool to measure physical activity, their high cost (US $450+), accompanying hardware and software requirements and associated data handling demands make

them relatively un-user friendly. Pedometers on the other hand are simple to use, inexpensive and produce user friendly output (steps taken, steps/day). The accumulated data on pedometers indicates there is a strong correlation (median r = 0.86) between pedometer and accelerometer output indicating that the output of one is representative of that of the other (344). Pedometers also correlated strongly (median r = 0.82) with time in observed activity, moderately (median r = 0.68) with different measures of energy expenditure and weakly (median r = 0.33) with self-reported physical activity and time spent sitting (median r = -0.38). Their construct validity was less impressive but still with positive relationships regarding indicators of fitness ranging from weak (median r = 0.22 for estimated VO_{2max}) to moderate (median r = 0.68 for 6 min walk test) (345). Many previous studies on bone mass and exercise have only examined leisure time physical activity. Pedometers provide an estimate of all weight-bearing activity throughout the entire day - all of which is likely to be important when considering bone mass as an outcome.

Kitagawa *et al* conducted the only study to date looking at pedometer measured steps per day and bone mass (346). In late post menopausal Japanese women, they demonstrated a quadratic relationship between steps per day and bone mass as measured by quantitative ultrasound. Walking activity up to approximately 12,000 steps/day, was positively associated with the age and/or weight adjusted ultrasound measurements, above which additional steps had no positive effect.

In summary, observational studies have shown walking is associated with a reduced fracture risk in men and women. Walking may also improve women's spine aBMD by small amounts but demonstrates no effect at the hip or for men's bone mass. Studies on habitual activity report beneficial effects on bone mass but the majority have used questionnaires to assess walking which have a range of

limitations. To date, there have been no population based studies looking at objectively measured habitual ambulatory activity (predominantly walking) and bone mass.

Aim

The aim of the current study was to examine the cross-sectional and longitudinal relationship between pedometer determined ambulatory activity (PAA) and bone mass in a community dwelling sample of males and females, aged 50 – 80 years.

9.2 Materials and Methods

Subjects

This study was conducted as part of the Tasmania Older Adult Cohort study (TASOAC) as described in Chapter 3. Briefly, from 2002-05 men and women between the ages of 50 and 80 years were randomly selected from the electoral role in Southern Tasmania. Subjects who were institutionalised were excluded from the study. Approximately two years later, eligible participants from Phase 1 (n=1071) were re-contacted and asked to participate in Phase 2 of the study. 92% of eligible participants returned for phase 2 with the breakdown of participants who were withdrawn displayed in Figure 9.1. Reasons for not returning included having died (n=16), moved interstate or overseas (n=14), institutionalized (n=1), joint replacement (n=15), physically unable (n=16) and other reasons (n=15). 58 subjects refused to continue and we were unable to trace 4 subjects. Lastly, 57 subjects were ineligible as they did not have a baseline MRI scan.

Descriptive variables

Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer (Invicta, Leicester, UK). Weight was recorded to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) that were calibrated using a known weight prior to each testing session. Body mass index (BMI) was calculated in kg/m^2 (for weight/height). Data was also collected on medication use (number, type and dose), smoking status (ever, former and current), and alcohol and calcium consumption (grams and milligrams per day respectively derived from a food frequency questionnaire) in 2002/04 and 2005/06 by self-administered questionnaire. Serum 25-hydoxyvitamin D [25(OH) D] was measured using a radio-immunoassay kit (DiaSorin, Stillwater, MN, USA). Blood (fasting) was collected on initial presentation to the clinic. The intra-assay and inter-assay precisions of these assays are 6% and 15% respectively. Menopause status was also recorded (premenopausal, postmenopausal, currently going through the menopause).

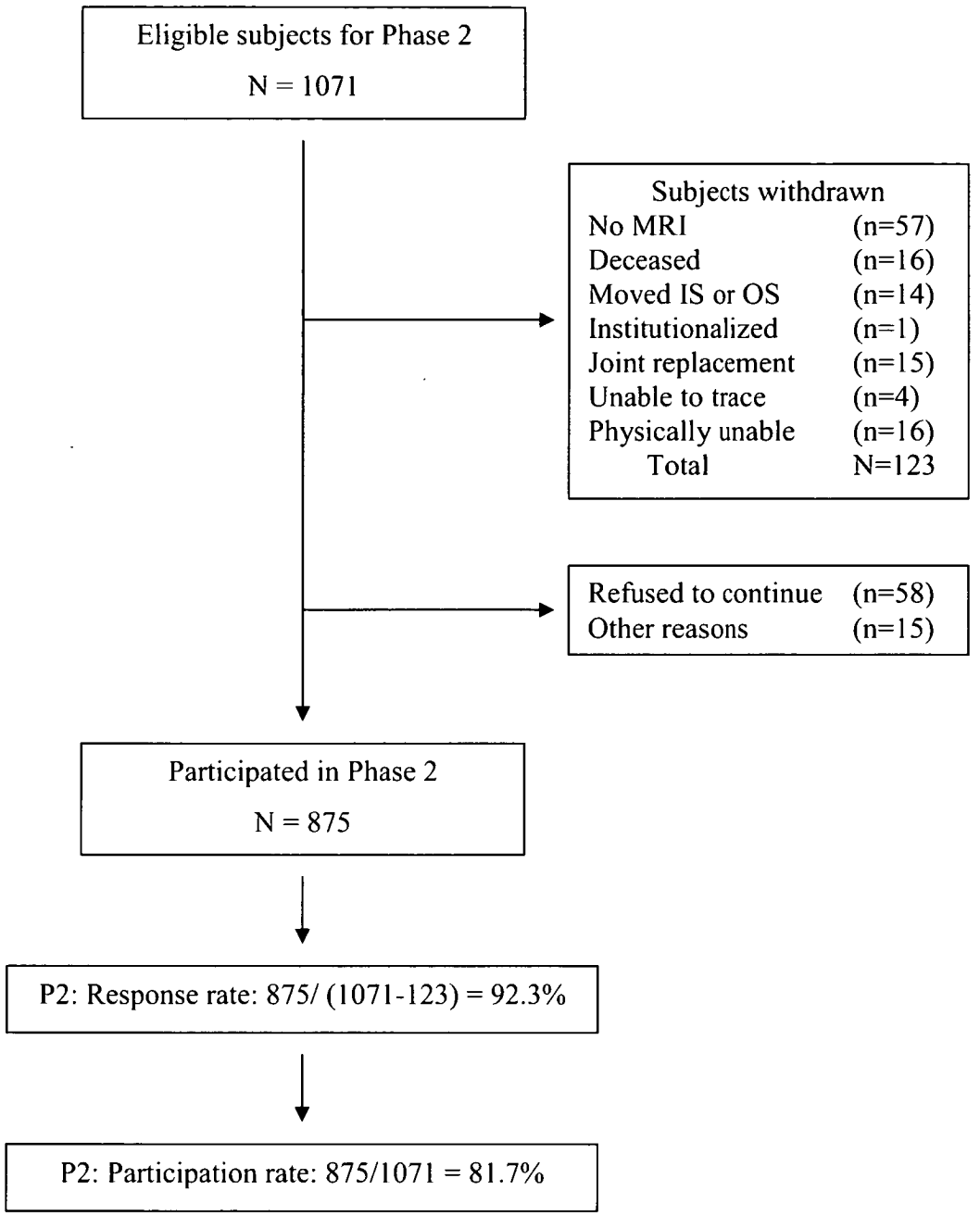

Figure 9.1. Flow chat of TASOAC participation for Phase 2.

Steps per day

We assessed steps per day using pedometers at both baseline and follow-up. At the first clinic visit Omron pedometers (HJ-002, Tokyo, Japan) were issued, and for the second visit we issued Yamax pedometers (Digi-walker SW-200, Yamax,

Tokyo, Japan). Participants were instructed to wear the pedometer on their dominant side for seven consecutive days except when bathing, sleeping or performing water based activities, and follow their normal daily routine. A log was kept indicating when the device was worn and removed and the step count for each day (see Appendix 1). To account for any seasonal variation in step counts, subjects were mailed a second pedometer six months after completing the one issued at the clinic visit. The same protocol was completed at follow-up. As such, each participant had two seven week pedometer logs for both baseline and follow-up. Based on pedometer logs, the duration of pedometer wear for each day was calculated. Days in which the pedometer was worn for a minimum of 8 hours were considered valid measurement days. In our analysis, mean steps were calculated as the mean of the four pedometer logs, with a minimum of four valid wear days (from each log).

It is well established that Omron pedometers over estimate actual steps taken. As such, a correction factor was derived for the Omron pedometers to make them analogous with the readings from the Yamax pedometers. To derive a correction factor, we had 22 participants wear both an Omron and Yamax pedometer at the same time for seven days. We then used the mean and standard deviation to transform the Omron distribution to the Yamax distribution:

$$x_y = (\frac{x_o - \bar{x}_0}{s_o}) \cdot s_y + \bar{x}_y$$

In our sample, Omron pedometers were higher than the Yamax readings by approximately 10%.

Bone mass assessment

Bone mass was assessed in the subjects at both time points using dual energy x-ray absorptiometry (DXA) at the lumbar spine and right hip (Delphi Hologic,

Waltham, MA). Bone mass was examined as areal bone mineral density (aBMD). Precision estimated *in vivo* are 2-3% in our hands. The longitudinal coefficient of variation for our machine between 2002 and 2007 using daily measurements of a spine phantom was 0.39% for aBMD.

Statistics

Students t-tests were used for comparisons of means for normally distributed data and Mann-Whitney U test was used for skewed data. For where the outcome was binary, Chi-square test was used. To incorporate the repeated-measures study design and take into account the correlated readings within individuals, the association of pedometer determined ambulatory activity (PAA) with bone mass was evaluated using linear mixed models with individual-specific random intercepts. Possible confounding factors (age, sex, BMI, vitamin D, bisphosphonate use, calcium and alcohol intake and smoking) were adjusted for. Age squared was found to be a significant predictor of changes in aBMD and included in both models. Routine diagnostics were checked to ensure model validity. A p-value less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed on Intercooled Stata 10.0 for windows (StataCorp LP).

9.3 Results

A total of 872 subjects had measures taken at baseline and approximately 2.6 years later. 652 subjects had complete pedometer data. Demographic and study factors of both participants in the current study, and those lost to follow-up are presented in Table 9.1. Compared to the study participants, those lost to follow-up contained a lower proportion of males, had an older mean age by approximately 2

years, were shorter, had a lower PAA and lower vitamin D level and also displayed a lower hip aBMD. Other demographic factors such as BMI, smoking habits, bisphosphonate use and spine aBMD were not significantly different between subjects retained and those lost to follow-up.

Table 9.1. Characteristics of the study population and those lost to follow-up

	Participants (n=875)	Lost to follow-up (n=224)	*P* value*
Sex (% males)	51	41	0.02
Age (years)	62.7 ± 7.3	64.4 ± 8.2	0.003
Height (cm)	167.5 ± 9.0	165.0 ± 8.8	<0.001
Weight (kg)	78.0 ± 14.5	77.7 ± 16.7	0.79
BMI (kg/m^2)	27.8 ± 4.6	28.4 ± 5.3	0.05
PAA (steps/day)	8571 ± 3249	7691 ± 3271	<0.001
25 (OH) D	53 ± 19	49 ± 17	<0.001
Calcium intake (mg/day)	918 ± 330	888 ± 374	0.22
Alcohol intake (g/day)†	7.8 (1.1 – 23.3)	5.0 (0.5 – 18.7)	0.09
Smoking: former/current (%)	38 / 11	40 / 15	0.23
Bisphosphonate use (%)	2	4	0.20
Women on HRT (%)	25	25	0.98
Hip aBMD (g/cm^2)	0.97 ± 0.15	0.94 ± 0.17	0.01
Spine aBMD (g/cm^2)	1.01 ± 0.17	1.00 ± 0.19	0.21

BMI: body mass index; PAA: pedometer determined ambulatory activity; HRT: hormone replacement therapy; aBMD: areal bone mineral density. The results are reported as percentage for binary variables, and the mean (standard deviation) for continuous variables. †Median and interquartile range reported due to skewed distribution. *Subjects vs. lost to

follow-up by Student's *t*-test except for alcohol, where Mann-Whitney U test was used and percentages where Chi-square test was used.

At baseline, PAA were positively associated with hip aBMD. An age-steps interaction was found, thus the beta coefficients for PAA and hip aBMD were plotted against the mid point of each age quartile (Figure 9.2). At the third age quartile mid point (65.2 yr) it can be seen that the effect of PAA on hip aBMD was both positive and significant; the effect is increased further again for the next age quartile midpoint (74.8 yrs).

We found no step-time interaction but there was an age-steps interaction ($p<0.001$) so there was a change in impact of PAA over time (as age increased). Hip aBMD point estimates are displayed in Table 9.2 for both baseline and follow-up. At baseline, estimated hip aBMD for a 65 year old male was increased by as little as 0.5% to as much as 1.8% for moving up a quartile of PAA. For a 65 year old female, the effect ranged from 0.6% to 1.4%. The percent difference between the lowest and highest quartile was 3.1% for both sexes. At follow-up, the percent change in estimated hip aBMD for a 65 year old increasing quartiles of PAA was similar (males: 0.7% to 1.7%, females: 0.4% to 1.7%). The percent difference between the lowest and highest quartile was 3.9% for males and 3.9% for females. For a 75 year old subject, the effect of increasing PAA had a greater beneficial effect. At baseline, the percent difference between quartiles of PAA ranged from 1.2% to 2.9% for males and 1.3% to 6.4% for females, and the difference between the lowest and highest quartiles was 5.9% for males and 9.4% for females. At follow-up, the percent difference between quartiles ranged from 1.1% to 2.2% for males and 1.1% to 4.5% for females, and the difference between the lowest and highest quartiles of PAA was 5.4% for males and 7.4% for females.

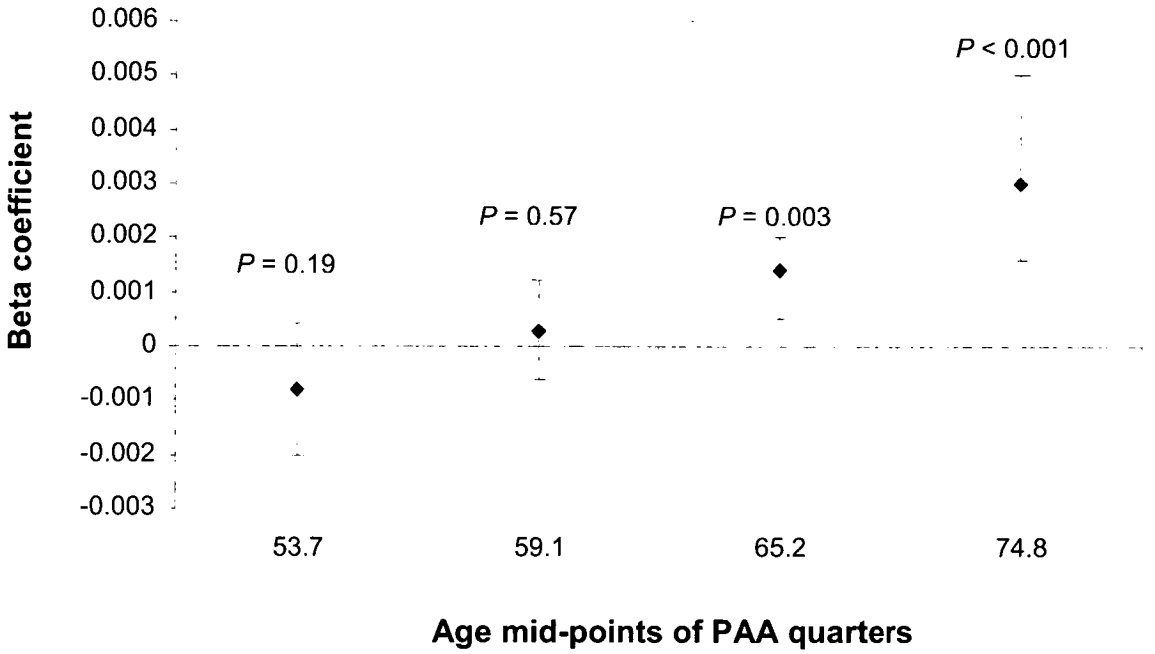

Figure 9.2.Cross-sectional relationship between PAA quarter at each age mid-point (per 1000) and hip aBMD. Error bars are confidence intervals. Adjusted for age, sex, BMI, smoking status, alcohol intake, 25(OH)D and bisphosphonate use. Mean daily steps are positively related to hip aBMD with the effect increasing with age.

Table 9.2. Point estimates for hip aBMD at baseline and follow-up by PAA at each age quartile mid-point for males and females*

Midpoint of PAA quarters	Point estimates							
	53.6 yr		59.1 yr		65.2 yr		74.7 yr	
	Males	Females	Males	Females	Males	Females	Males	Females
HIP baseline								
Q1	0.639	0.516	0.625	0.502	0.609	0.486	0.578	0.457
	(0.573, 0.705)	(0.452, 0.580)	(0.560, 0.690)	(0.440, 0.565)	(0.545, 0.673)	(0.424, 0.548)	(0.514, 0.643)	(0.395, 0.520)
Q2	0.635	0.513	0.626	0.503	0.614	0.491	0.588	0.464
	(0.568, 0.701)	(0.450, 0.577)	(0.561, 0.691)	(0.441, 0.566)	(0.550, 0.678)	(0.429, 0.553)	(0.523, 0.653)	(0.401, 0.527)
Q3	0.634	0.512	0.627	0.504	0.617	0.494	0.595	0.470
	(0.567, 0.700)	(0.447, 0.576)	(0.562, 0.691)	(0.441, 0.567)	(0.553, 0.682)	(0.431, 0.556)	(0.530, 0.661)	(0.407, 0.534)
Q4	0.629	0.506	0.629	0.506	0.628	0.501	0.612	0.500
	(0.562, 0.697)	(0.440, 0.572)	(0.563, 0.694)	(0.442, 0.569)	(0.562, 0.693)	(0.438, 0.564)	(0.544, 0.680)	(0.431, 0.568)
HIP follow-up								
Q1	0.622	0.499	0.607	0.485	0.587	0.467	0.554	0.434
	(0.556, 0.687)	(0.436, 0.562)	(0.543, 0.671)	(0.422, 0.547)	(0.523, 0.651)	(0.406, 0.529)	(0.490, 0.618)	(0.372, 0.497)
Q2	0.621	0.498 (0.435,	0.609	0.486	0.596	0.473	0.566	0.441
	(0.555, 0.686)	0.561)	(0.545, 0.673)	(0.424, 0.549)	(0.532, 0.660)	(0.411, 0.535)	(0.501, 0.631)	(0.378, 0.503)
Q3	0.620	0.497	0.611	0.488	0.600	0.475	0.572	0.446
	(0.554, 0.685)	(0.434, 0.561)	(0.547, 0.675)	(0.426, 0.550)	(0.536, 0.665)	(0.413, 0.537)	(0.507, 0.637)	(0.383, 0.509)
Q4	0.618	0.496	0.615	0.491	0.610	0.483	0.584	0.466
	(0.551, 0.684)	(0.432, 0.560)	(0.550, 0.679)	(0.429, 0.554)	(0.545, 0.676)	(0.420, 0.545)	(0.518, 0.651)	(0.401, 0.532)

*Adjusted for time, age, ageXsteps, sex, BMI, smoking status, bisphosphonate use, alcohol intake, calcium intake and 25(OH)D

Longitudinally, there was no association between PAA and spine aBMD in males possibly due to osteophytosis as spine aBMD increased slowly after age 63 (data not shown). For females, increased PAA was associated with reduced loss of bone mass over time. Again, the effect was constant but not additive. Point estimates for spine aBMD are displayed in Table 9.3. For spine aBMD, cross-sectionally, there was a positive relationship between PAA and spine aBMD for females: $\beta = 0.0023$ (95% CIs: 0.0013, 0.0041) $p<0.001$, but not for males: $\beta = 0.0001$ (95% CIs: -0.001, 0.001) $p = 0.87$. For females at baseline and follow-up, estimated spine aBMD was increased by as little as 0.8% for moving up a quartile of PAA, to as much as 2.9%. The difference in spine aBMD between the lowest and highest quartile was 5.1% at baseline and 4.2% at follow-up.

Table 9.3. Point estimates for spine aBMD at baseline and follow-up by PAA for males and females of mean age*

Mid point of PAA quarters	Point estimates	
	Males	Females
SPINE baseline		
Q1	0.808	0.703
(m: 3365, f: 3890)	(0.724, 0.892)	(0.622, 0.785)
Q2	0.809	0.712
(m: 7372, f: 6969)	(0.725, 0.893)	(0.631, 0.793)
Q3	0.809	0.718
(m: 9902, f: 9281)	(0.725, 0.893)	(0.637, 0.799)
Q4	0.810	0.739
(m: 17 018, f: 17 145)	(0.725, 0.894)	(0.658, 0.821)
SPINE follow-up		
Q1	0.813	0.690
(m: 2635, f: 3016)	(0.729, 0.896)	(0.608, 0.771)
Q2	0.813	0.698
(m: 6181, f: 6057)	(0.729, 0.897)	(0.617, 0.779)
Q3	0.813	0.704
(m: 8479, f: 8197)	(0.730, 0.897)	(0.622, 0.785)
Q4	0.814	0.719
(m: 17 561, f: 13 778)	(0.730, 0.899)	(0.637, 0.800)

*Adjusted for age, age^2, sex, sexXsteps, sexXage, bisphosphonate use, calcium intake, BMI, smoking status, alcohol intake and 25(OH)D

9.4 Discussion

To our knowledge this is the first longitudinal study to examine objectively measured ambulatory activity and hip and spine bone mass. Our results show that PAA was largely positively associated with hip bone mass, with the effect being strongest for people over the age of 65. Our results also confirm that in females, daily steps are associated with spine aBMD, with the relationship being constant but not additive over time.

Pedometer measured steps do not distinguish between type or intensity of activity. Given the age of our participants and that the majority of our data is from 28 full days of wear, it would not be unreasonable to assume that most steps recorded were accrued from walking. Similarly, we asked participants to follow their normal daily routine to estimate their habitual activity. Quantifying the effects of habitual exercise is important given the issue of compliance in training studies and that in older people, cessation of exercise is the Achilles heel of exercise induced bone mass gains. Furthermore, exercise, like many things, is far more likely to be continued if it becomes a habit (347). Thus, our data is based predominantly on older people's habitual walking patterns.

Hip fractures are the most serious fracture due to their association with increased morbidity and mortality (348), in addition to being a large financial burden on society. We found higher PAA was associated with higher hip aBMD particularly for those aged over 65 years. The age interaction is important given fracture incidence rises sharply after age 65 years and demonstrates the importance of older people continuing weight-bearing activity. We found no step-time interaction, that is, PAA did not provide an additional annual impact on hip aBMD. As such, stepping helped minimize bone mass loss over time but did not increase it, which is concordant with

previous reports that suggest exercise may not increase bone formation but may prevent bone resorption (319,349). Although the effects are modest, it is important to remember that aBMD is only one determinant of fracture risk. Ambulatory activity may also increase lean mass, thereby improving muscle strength (350), improve balance (351,352) and help maintain people's independence. Therefore, the small effect PAA exerts on bone mass is likely to be compounded into greater effects when considering reduced fracture risk as a whole. Indeed, Cooper and colleagues (300) showed that activities of daily living (including standing, walking, climbing stairs, carrying, housework, and gardening) were protective against hip fractures.

The majority of research on walking and bone mass has been undertaken in post menopausal women. Our data showed sex did not modify the relationship between steps and hip aBMD, thus the positive effect of steps was the same in males and females. Two previous studies looking at men found that regular aerobic exercise (80) and walking (79) had no measurable effect on bone mass. The contradictory findings between our and the aforementioned studies may relate to the age of participants. The men in both previous studies were less than 65 years old, which we found to be the age at which PAA began to have a significant effect on bone mass. This may similarly be the reason why few studies in females have also shown an effect at the hip. The majority of postmenopausal women who took part in walking interventions, were younger than 65 years. In fact, if we look at the randomised controlled trial that included older participants separately (322), walking appeared to have a beneficial effect on femoral neck bone mass. Unlike younger women where exercise may need to be performed at a relatively high intensity to see improvements, our data, along with others suggests that for older people, the joint reaction forces and

ground reaction forces experienced from ambulatory activity are adequate to maintain hip bone mass.

There was a continuous positive effect of PAA on spine aBMD in females. Unlike the hip, PAA did not appear to interact with age suggesting for females stepping was beneficial for spine aBMD through the entire age range studied. This is concordant with two meta-analyses (78,81) that suggested walking interventions could have a small but positive effect on the spine bone mass of post-menopausal women. Although most women were post menopausal, our analyses included pre, peri and post menopausal women, however adjusting for menopausal status or HRT use did not change our results. Likewise, examining post menopausal women alone showed almost identical results to the analysis presented but it remains possible that hormonal factors are relatively more important in men and women aged 50-65 years.

Our data showed that PAA was not associated with spine aBMD in males. In our sample, males spine aBMD decreased slowly until approximately age 63 and then increased steadily thereafter, similar to the findings of Huuskonen *et al* (80). The increase in aBMD is most likely due to the influence of arthritic changes (353) making the spine an unreliable site for follow-up aBMD measurements in men. The femur therefore, appears to be the most meaningful measurement in men.

The suggested amount of walking required to increase aBMD has ranged from 12.1 km/wk (331) to 18.5km/wk (327). In the current study, the mean number of steps were ~8500 per day at baseline (59 500 per week). When multiplied by stride length (0.62 m) as measured in an similar cohort (354), this equated to approximately 5.3 km/day (37.1 km/wk). The great disparity between the previous reports and ours is likely due to the fact the previous reports are referring to walking additional to participants' normal daily activity, whereas the distance in our study is a reflection of

participants' activity for the entire week and indicates people can maintain their bone mass in the course of day to day activities, with the more the better. Similarly, we showed moving up one quartile of PAA could increase aBMD by as little as 0.4% to as much as 6.4% (hip aBMD for a 75 year old women going from the 3rd quartile of PAA to the 4th). In our sample, 1 SD of aBMD corresponded to approximately 14-17% of total aBMD indicating that by increasing one quartile of PAA, fracture risk could be reduced by up to 30%. The difference between the highest and lowest quartile of PAA was as great as 9.4%, again for a 75 year old women. This difference would correspond to an approximate 50% reduction in hip fracture risk.

The current study had a number of potential limitations. Firstly, although the response rate was reasonable at 57% of which nearly 90% returned for the second visit, those retained were younger and therefore reflected in the other demographic characteristics (i.e. higher hip aBMD). The implications of having a younger sample may have reduced our heterogeneity and lead to a decrease in the strength of associations reported. Our sample was limited to community dwelling participants, thus our results may not apply to those persons institutionalised. Similarly, a relatively healthy population was recruited, thus the heterogeneity of our sample may be reduced, resulting in a weakening of associations reported. Thirdly each bone scan has measurement error associated with it which will weaken associations over 2.6 yrs suggesting longer term follow-up is desirable. Fourthly, although the use of pedometers is a strength of this study, they still have their limitations. One limitation being they do not measure intensity. Previous studies suggest that exercise intensities above 74% of VO_{2max} (327) or 90% of maximal heart rate (323) are sufficient for preservation of aBMD in women. Similarly, Frost's mechanostat 'set-point' theory (355) and several animal (356) trials suggest that loads which are relatively high in

magnitude, applied rapidly and which are of an unusual distribution are most effective for stimulating an osteogenic response, whereas duration of loading is not as important. Consequently, future studies may benefit from the use of accelerometers to elucidate the volume vs. intensity question. Some activity may have also been missed such as water based activities. Considering we monitored participants over the entire day, the influence of such activity is likely to be minimal. Lastly, we used different pedometer brands for baseline and follow-up. Omron HL-105 have been reported to overestimate step counts at normal walking speeds by up to 20% (357). However piezoelectric pedometers such as the Omron HJ-105, have been shown to be more accurate than spring-levered pedometers (e.g. Yamax SW-200) at the slower walking speeds typical among older adults (358). Nevertheless, for comparability purposes, we "standardised" the Omron estimates to the Yamax estimates based on data from a sub-set of people who wore both.

In conclusion, PAA had a small but continuous positive association with hip aBMD in both sexes which appears most important in those over 65 years of age. The associations for spine aBMD were both weaker and inconsistent suggesting site specific effects.

CHAPTER 10: SUMMARY AND FUTURE DIRECTIONS

SUMMARY

Falls, osteoarthritis and osteoporosis, including resulting fractures constitute a major health problem, as large contributors to illness, pain and disability. They occur frequently, placing a high economic burden on society. However they need not be thought of as an inevitable part of growing old. By focusing on prevention and lifestyle changes, such as physical activity, as well as early diagnoses and appropriate treatment, much of the damaging impact of falls, and bone and joint disease may be avoided. In this thesis we have examined several aspects of these conditions and have presented novel and important findings that shed considerable insight onto the role that PA and exercise play in preventing osteoarthritis and osteoporosis.

In chapter 4, our cross-sectional study showed that it was self-reported functional ability and pain, and to a lesser extent, stiffness but not radiographic OA, that were significantly associated with physiological falls risk in a community living sample. Females who reported a WOMAC score $\geq$50 had more than a three-fold increase in fall risk score compared with women with WOMAC scores below this level. Males demonstrated a "dose response" association between WOMAC score and falls risk. Consistent results were observed for most of the WOMAC and falls risk subscales, including knee extension strength but with the exception of proprioception.

Chapter 5 presented the first study to describe the associations between fitness, physical activity, and knee structural change. In this longitudinal study we demonstrated that lower limb muscle strength was positively associated with both total cartilage volume and tibial plateau area change per year. In females, there was a deleterious relationship between PWC_{170} and annual change in lateral and total cartilage volume and tibial bone area. Changes in PWC_{170} were positively associated with annual changes in medial, lateral and total cartilage volume and there was a

beneficial association between annual change in lower limb muscle strength and change in lateral and total tibial plateau area annually. Strenuous exercise was associated with a reduction in the odds of defects progressing. These associations were modest in magnitude, typically explaining less than 4% of the variance in the data, but indicate that the relationship between physical activity and change in knee structure is complex and may have differential effects on bone and cartilage.

Chapter 6 was the first long term inception cohort study to demonstrate that physical fitness in childhood is associated with bone mass in adulthood, independent of adult fitness. This is most evident in females and pre or early pubertal children and confirmed the evidence from retrospective and short term intervention studies that early childhood is an opportune stage of growth when the skeleton is most responsive to exercise. In addition, childhood BMI, was predictive of adult bone mass in males suggesting skeletal loading by body weight also had modest long term benefits

Chapter 7 was the first prospective study to report that a single bone densitometry scan at age eight can predict upper limb fracture risk in males and females during puberty. This ability for long term fracture prediction (an average of 4.3 years later) is important, especially given the magnitude was similar to short term studies. This suggests that bone density tracks throughout adolescence and that bone strength may remain relatively constant through this period despite the rapid change in bone size.

In Chapter 8 we examined this notion of tracking. As far as we are aware, it was the first longitudinal study to examine the tracking of bone density at the hip, spine and total body from the prepubertal years to late adolescence in males and females. The results confirmed and extended on previous reports (176,265,285,286) and demonstrated that BMD and BMAD track strongly from the prepubertal years to

late adolescence when peak bone mass is largely attained (175,176). Despite the strong tracking, a number of factors either were significantly associated with or had modest associations with altered tracking over this period. Lean mass, fitness, sports participation and having been breastfed were related to *positive deviation*, while change in fat mass and ICS use were related to *negative deviation*.

In Chapter 9 we examined objectively measured ambulatory activity and hip and spine bone mass in a longitudinal study. Our results showed that ambulatory activity was positively associated with hip bone mass, with the effect being strongest for people over the age of 65. Our results also confirmed that in females, daily steps are associated with spine aBMD, with the relationship being constant over time but not additive.

FUTURE DIRECTIONS

In Chapter 4, our finding that pain and physical dysfunction was associated with falls risk, was cross-sectional in nature. Thus further investigations in a longitudinal setting are required to determine if increased risk of falling is predicted by pain and physical dysfunction. Further to this, a RCT of pain control such as analgesic use and falls risk would provide stronger evidence for causality. We reported on a community dwelling population who were at a mild risk of falling. As such, further work is needed to determine if similar relationships are also present in those at a high risk of falling and in other populations (i.e. the institutionalised). Similarly, our outcome was falls risk, thus our findings should be replicated with data on actual falls. The WOMAC subscales were associated with falls risk independent of OA as assessed on X-ray. MRI allows more specific and sensitive quantification of joint pathology consistent with OA, thus it would be interesting to determine if pain,

functional dysfunction and stiffness are associated with falls risk independent of MRI findings like chondral defects, which have been shown to be associated with pain (359).

In Chapter 5 our findings were inconsistent, in that physical activity appeared to have both good and bad effects on the knee. Therefore, first and foremost, there needs to be replication of our study. Similarly, as we found no associations with physical activity as assessed by questionnaire, future studies should use objectively measured physical activity such as that from pedometers or accelerometers. Furthermore given OA recommendations and treatment are still based on X-ray findings, a prospective study is needed that examines the long-term relationship (i.e. 5+ years) between physical activity and radiographic OA and MRI findings simultaneously. Such a study would be interesting in both elite populations from varying sports, similar to that by Kujala *et al* (125), but also in those who are not as athletically gifted; the majority of the population. Our study did suggest muscle strength was positively associated with cartilage volume in accordance with previous reports. As such, if our findings can be replicated, the next step is to conduct a RCT on the effects of a muscle strengthening intervention on joint structural change. Such a study would be most beneficial in those presenting with knee pain. Lastly, there is a need for prospective studies on physical activity and hip OA, as to date, there have been none. Like the knee, methods have been established for hip articular cartilage quantification from MRI scans and would be a valuable outcome in future studies on physical activity.

In Chapter 6 we provided the strongest evidence to date that childhood activity can have positive long term effects on bone mass. Much work is still needed to determine the magnitude, rate, distribution and number of loading cycles required to

induce clinically meaningful changes that are maintained if exercise is ceased. Future studies should incorporate diverse measures such as MRI and peripheral computed quantitative tomography at several bone regions to elucidate the full impact of an intervention on bone strength. Although there have been many interventions in children that have shown an effect on bone mass, there has not been a meta-analysis of published studies which may be useful in elucidating the type, frequency and intensity of activity that would most beneficial to put into practice. Further to this, the most valuable information would be the long-term follow-up of children who have participated in interventions such as "Bounce at the Bell". Even without this, interventions that increase fitness though skeletal loading should be implemented sooner rather than later, particularly given the sedentary nature of today's children.

In Chapter 7 we showed that a single DXA scan at age 8 was a good predictor of subsequent fracture. Given we now know childhood fractures are related to underlying bone fragility, it would be worthwhile to see whether childhood exercise interventions aimed at increasing bone mass, could also protect children from subsequent fractures during childhood and adolescence. More work is still needed however to elucidate what, if any, environmental factors also contribute to incident fractures in childhood and adolescence. Similarly, overweight children seem to be at more risk of fracture which is particularly relevant given the obesity epidemic in children today. Therefore studies examining weight loss in overweight children should include fracture as an outcome to determine if weight loss is associated with a reduced risk of fracture.

The constancy of fracture prediction following a single DXA scan suggests bone mass tracks. In Chapter 8 we confirmed and extended on previous reports to show bone measures tracked from childhood to adolescence. We can do two

important things from here. Firstly, we need to determine if we can use a child's DXA scan to resolve any underlying skeletal fragility and protect them from subsequent fractures. That is, can we measure a child, treat them, and identify outcomes of interest (i.e. increased aBMD and/or reduced fracture rate). Along the same lines, we need studies of the value of early bone mass screening, in terms of the effect on individual choices (i.e. uptake of exercise). Secondly, future research is needed to show a cost effective approach to identifying those at risk of developing osteoporosis and treating them. Examples may be, examining children with a parent known to have low bone mass or siblings of a child who has had a low trauma fracture. Further to this, there needs to be policy development with respect to early detection of osteoporosis risk.

In Chapter 8 we also identified predictors of altered tracking, although this was not the primary aim of the paper and was therefore considered an exploratory analysis. As such, further investigations in larger studies are needed. In particular, ICS use at high doses appeared to be detrimental and must be addressed in larger samples. Future work should also look at vitamin D levels to determine what effect, if any, it has on a child's ability to move to a higher percentile of bone mass.

In the last chapter of this thesis, we reported ambulatory activity was associated with hip bone mass especially in those aged over 65 years. As such, a RCT should be conducted looking at the effects of prescribed walking and bone mass specifically in this older age group to both confirm and extend on our findings. Further comparisons could also be undertaken using another objective measure of activity like accelerometers. This would help elucidate the question surrounding intensity of activity required for older people to increase BMD. Bone mass is only one predictor of fracture, thus the ideal study would be to objectively measure physical

activity with a pedometer or accelerometer, and follow many people over the several years with fracture as the end point. Lastly, it would be valuable to carry out a cost analysis of activity known to increase bone mass vs. anti-resorptive drugs.

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APPENDICES

Appendix 1: Pedometer diary

TASOAC PEDOMETER DIARY Phase 2 Round 1

Name.....TASOAC ID☐☐☐☐☐☐☐ Pedometer number☐☐

☐

Sensitivity number.....☐ **Remember to reset Pedometer Daily.**

Day	Date	Start time	End time	Display number	Time spent NOT wearing pedometer Whilst participating in physical activity	Name activity participated in whilst not wearing pedometer	List any circumstances which may have affected pedometer reading
1							
2							
3							
4							
5							
6							
7							